Facile Preparation of Perfluoro-*tert*-butyl Ethers by the Mitsunobu Reaction

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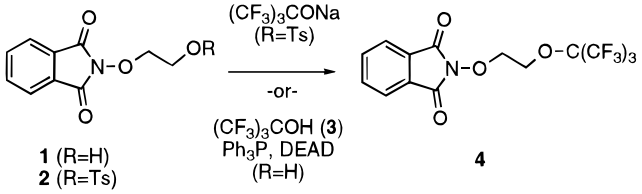
In the course of our efforts toward incorporating functionally modified nucleotide triphosphates in the generation of oligonucleotide libraries for screening,[1] we were in need of a fluorinated hydroxylamine derivative such as **4** (Scheme 1). Two recent reports from the Falck laboratory[2] describing the preparation of fluoroalkyl ethers by a modified Mitsunobu reaction have prompted us to disclose our complementary findings in this area.

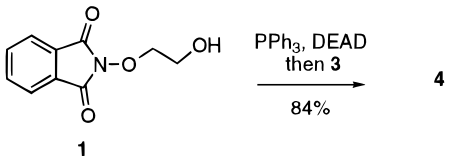
Although perfluoro-*tert*-butyl (PFTB) alcohol (**3**) has recently become commercially available (Aldrich), a review of the literature reveals only a single contribution describing alkylations of this alcohol to form the corresponding PFTB ethers.[3] The protocol calls for generation of the sodium salt of the alcohol and subsequent treatment with alkyl halides in refluxing methyl ethyl ketone for several days. In this way, moderate to good yields of the corresponding PFTB ethers were achieved. In our hands, however, treatment of tosylate **2** with $NaOC(CF_3)_3$ (in the presence of KI) under these conditions resulted in a mere 11% yield of the desired ether. In light of this low yield and the cumbersome reaction conditions, we were prompted to consider alternative etherification methodologies.

The triphenylphosphine/diethyl azodicarboxylate (TPP/DEAD) protocol, known as the Mitsunobu reaction, has been employed to alkylate a variety of nucleophiles with primary and secondary alcohols.[4] Treatment of an alcohol with TPP/DEAD results in the formation of a reactive triphenylphosphonium intermediate which is displaced by the conjugate base of any of a number of acids added subsequently to the reaction mixture. Carboxylic and phosphoric acids, phenols, imides and *N*-hydroxyimides, halide and azide salts, heterocyclic amides, and activated carbon acids have successfully been employed as Mitsunobu nucleophiles, however, with the exception of *intra*molecular etherifications to form 3- to 7-membered rings, alcohols are typically not suitable. This is presumably due to the relative pK_a's of most alcohols and the carboxyhydrazine anion intermediate which deprotonates the conjugate acid of the nucleophile. Typically, alcohols ($pK_a = 16-19$)[5] are not acidic enough

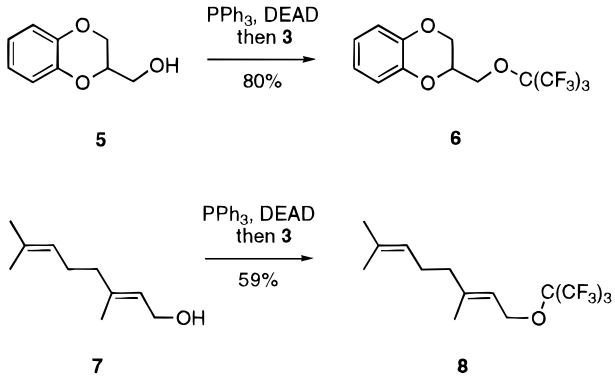
Scheme 1



Scheme 2



Scheme 3



to be deprotonated to any appreciable extent and are not sufficiently reactive to displace the phosphonium leaving group to form ethers (except in the kinetically favorable case of ring formation). We predicted, however, that PFTB alcohol, substantially more acidic ($pK_a = 9.5$)[6] than aliphatic alcohols due to the electron-withdrawing effect of the nine fluorine atoms, would be deprotonated under the Mitsunobu reaction conditions and that the resultant alkoxide would displace the oxophosphonium leaving group under milder conditions than the previous alkylation protocol. In fact, treatment of a 0 °C THF solution of primary alcohol **1** with 1.5 equiv of TPP and 1.5 equiv of DEAD, followed after 5 min by 1.5 equiv of PFTB alcohol, resulted in clean conversion to the desired PFTB ether **4** within less than 30 min (Scheme 2). Chromatographic purification of **4** afforded analytically pure material in 84% yield.

Perfluoro-*tert*-butyl ethers of two of other alcohol substrates were similarly prepared (Scheme 3). Benzodioxan derivative **5** was converted to PFTB ether **6** in 80% yield, while geraniol (**7**) was converted to ether derivative **8** in 59% yield.

The few examples described here, along with the complementary fluoroalkyl etherifications reported by the Falck group,[7] suggest that the Mitsunobu fluoroetherification represents a potentially useful methodology for the formation of a synthetically challenging class of compounds.

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(2) (a) Falck, J. R.; Yu, J.; Cho, H.-S. *Tetrahedron Lett.* **1994**, *35*, 5997−6000. (b) Cho, H.-S.; Yu, J.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 8354−8355.

(3) Pavlik, F. J. Perfluorotertiaryalkyl Ethers. U.S. Patent no. 3,981,928.

(4) (a) For a comprehensive review of the Mitsunobu Reaction, see: Hughes, D. L. *Org. React.* **1992**, *42*, 335−656. (b) For recent applications in carbon−carbon bond formation, see: Falck, J. R.; Yu, J. *Tetrahedron Lett.* **1992**, *33*, 6723−6726. Yu, J.; Cho, H.-S.; Falck, J. R. *J. Org. Chem.* **1993**, *58*, 5892−5894. (c) For a recent application in the formation of aryl glycosides, see: Roush, W. R.; Lin, X. *J. Org. Chem.* **1991**, *56*, 5740−5742.

(5) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry;* Harper and Row: New York, 1987; Third Ed, p 300.

(6) Henne, A. L.; Francis, W. C. *J. Am. Chem. Soc.* **1953**, *75*, 991−992.

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Experimental Section

Reactions were performed in flame-dried glassware using anhydrous solvents. Proton, ^{19}F, and ^{13}C NMR spectra were measured in the indicated solvents at 300, 282, and 75 MHz, respectively. Proton and ^{13}C NMR spectra were calibrated against internal standards (TMS and/or solvent), and ^{19}F NMR spectra were calibrated against an external standard (CF_2Cl_2).

***O*-(2-Hydroxyethyl)-*N*-hydroxyphthalimide (1).**[8] To a stirred solution of 40.3 g (0.25 mol) of *N*-hydroxyphthalimide in 500 mL of DMF was added 22.3 g (0.27 mol) of NaOAc. The dark red solution was stirred for 15 min, and then 19.1 mL (0.27 mol) of 2-bromoethanol was added via syringe. The mixture was heated to 60 °C, stirred for 16 h, and then concentrated *in vacuo*. The residue was dissolved in EtOAc and washed five to seven times with $NaHCO_3$ solution until none of the red to yellow color of the *N*-hydroxyphthalimide anion remained in the aqueous phase. The organic phase was dried over Na_2SO_4 and concentrated to afford 25.2 g (49%) of **1** as a white chalk: ^1H NMR (DMSO) δ 7.87 (br s, 4H), 4.82 (t, J = 4.2 Hz, OH), 4.17 (t, J = 4.8 Hz, 2H), 3.69 (q, J = 4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 165.20, 135.52, 129.32, 124.40, 80.17, 59.71. *Anal.* Calcd for $C_{10}H_9NO_4$: C, 57.95; H, 4.38; N, 6.76. Found: C, 57.89; H, 4.50; N, 6.60.

***O*-(2-(*p*-Toluenesulfonyloxy)ethyl)-*N*-hydroxyphthalimide (2).** To a stirred, 0 °C solution of 8.6 g (0.042 mol) of **1** in 80 mL of pyridine was added 9.52 g (0.05 mol) of TsCl. The mixture was left in the refrigerator at 4 °C for 48 h and then concentrated *in vacuo*. The residue was dissolved in EtOAc and washed twice with HCl solution (1:1 concentrated HCl:H_2O). The organic phase was dried over Na_2SO_4 and concentrated. The pale pink solid was triturated with Et_2O to afford 8.5 g (56%) of **2** as a white solid: ^1H NMR (DMSO) δ 7.87 (s, 4H), 7.79 (d, J = 8.4 Hz), 7.48 (d, J = 8.1 Hz), 4.36−4.31 (m, 4H), 2.42 (s, 3H); ^{13}C NMR (DMSO) δ 163.91, 145.95, 135.56, 132.80, 130.95, 129.29, 128.41, 123.99, 75.31, 68.73, 21.20. Anal. Calcd for $C_{17}H_{15}NO_6S$: C, 56.50; H, 4.18; N, 3.88. Found: C, 56.52; H, 4.31; N, 3.98.

***O*-(2-(Perfluoro-*tert*-butyloxy)ethyl)-N-hydroxyphthalimide (4): a. Alkoxide Alkylation Technique.**[3] To a stirred, 0 °C slurry of 0.13 g (5.53 mmol) of NaH in 10 mL of THF was added 0.77 mL (5.53 mmol) of perfluoro-*tert*-butyl alcohol (**3**). After 15 min, the mixture was concentrated *in vacuo*. The residue was dissolved in 20 mL of methyl ethyl ketone and this solution treated with 2.0 g (5.53 mmol) of **2** and 92 mg (0.55 mmol) of KI. The mixture was heated to reflux and stirred for 4 days. The reaction mixture was concentrated *in vacuo* and the residue dissolved in a minimum amount of dichloromethane and purified on a column of 250 mL of silica gel packed in hexanes (eluting with 250 mL each of 0, 10, 20, 30, 40, and 50% EtOAc/hexanes) to afford 0.27 g (11%) of **4** as a white chalk.

b. Mitsunobu Technique. To a stirred solution of 2.75 g (13.3 mmol) of **1** in 150 mL of THF was added 5.2 g (19.8 mmol) of Ph_3P. The solution was cooled to 0 °C and treated with 3.12 mL (19.2 mmol) of DEAD. After several minutes, 2.95 mL (21.2 mmol) of perfluoro-*tert*-butyl alcohol (**3**) was added. The cooling bath was removed, and the mixture was stirred for 15 min, after which time TLC analysis showed complete conversion of **1**. The reaction mixture was concentrated *in vacuo* and the residue applied to a column of 600 mL of silica gel packed in hexanes. The product was eluted with 500 mL each of 0, 10, 20, 30, 40, and 50% EtOAc/hexanes to afford 4.66 g (83%) of **4** as a white chalk: ^1H NMR (DMSO) δ 7.87 (br s, 4 H), 4.46−4.42 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 164.21, 135.44, 129.5, 124.32, 120.84 (q, J = 293.3 Hz), 80.3 (m), 76.25, 68.53; ^{19}F NMR (DMSO) δ 54.46. Anal. Calcd for $C_{14}H_8NO_4F_9$: C, 39.54; H, 1.90; N, 3.29. Found: C, 39.54; H, 2.03; N, 3.28.

2-((Perfluoro-*tert*-butyloxy)methyl)-1,4-benzodioxan (6). To a stirred, 0 °C solution of 0.65 g (3.9 mmol) of **5** in 40 mL of THF was added 1.54 g (5.9 mmol) of Ph_3P, followed by 0.92 mL (5.9 mmol) of DEAD. After 2 min, 0.87 mL (6.2 mmol) of perfluoro-*tert*-butyl alcohol (**3**) was added. The cooling bath was removed, and the mixture was stirred for 5 h and concentrated *in vacuo*. The residue was triturated with hexanes, and the filtrate was concentrated to afford 2 g of a yellow oil. This material was purified on a column of 100 mL of silica gel (eluting with 0, 5, 10, and 15% EtOAc in hexanes) to afford 1.2 g (80%) of **6** as a faint yellow wax: ^1H NMR ($CDCl_3$) δ 6.92−6.83 (m, 4H), 4.42−4.40 (m, 1H), 4.32−4.09 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 142.9, 142.5, 122.0, 121.8, 120.2 (q, J = 291 Hz), 117.35, 79.7 (m, J = 30 Hz), 70.83, 67.42, 64.39; ^{19}F NMR ($CDCl_3$) δ 74.7. Anal. Calcd for $C_{13}H_9O_3F_9$: C, 40.62; H, 2.36. Found: C, 40.81; H, 2.44.

Geranyl Perfluoro-*tert*-butyl Ether (8). To a stirred solution of 0.52 mL (3 mmol) of geraniol (**7**) in 15 mL of THF was added 1.18 g (4.5 mmol) of Ph_3P. The solution was cooled to 0 °C and treated with 0.71 mL (4.5 mmol) of DEAD. After several minutes, 0.67 mL (4.8 mmol) of perfluoro-*tert*-butyl alcohol (**3**) was added and the cooling bath removed. The mixture was allowed to warm to ambient temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue applied to a column of 100 mL of silica gel packed in hexanes. The product was eluted using 250 mL each of hexanes and 10% and 20% EtOAc in hexanes to afford 0.65 g (59%) of **8** as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 (dd, J = 7.0, 1.1 Hz, 1H), 5.09−5.05 (m, 1H), 4.51 (d, J = 7.0 Hz, 2H), 2.18−2.05 (m, 4H), 1.68 (s, 6H), 1.59 (s, 3H); ^{19}F NMR ($CDCl_3$) δ 70.22. Anal. Calcd for $C_{14}H_{17}OF_9$: C, 45.17; H 4.60. Found: C, 46.77; H 5.08.

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(7) Professor Falck reports etherifications using $(CF_3)_2CHOH$, $CF_3(CF_2)_6CH_2OH$, $(CF_3)_2PhCOH$, and CF_3CH_2OH as acidic alcohol nucleophiles under Mitsunobu (TPP/ DEAD) and modified Mitsunobu (Bu_3P, 1,1′-(azodicarbonyl)dipiperidine) conditions.[2a,b] We also observed alkylation of $CF_3CF_2CH_2OH$ and $C_6F_5CH_2OH$ with alcohol **1**; however, under our unoptimized conditions, these etherifications were not particularly efficient (21−36% yields). Falck describes the necessity for heating reactions employing less acidic fluoro alcohols (pK_a 11−13),[2a] and these data may suggest a pK_a threshold above which acids are not deprotonated to a sufficient extent for efficient Mitsunobu reaction to occur at ambient temperatures.

(8) For *N*-hydroxyphthalimide alkylation, see: Rougny, A.; Daudon, M. *Bull. Soc. Chim. Fr.* **1976**, 833−838.