Communications to the Editor

Preparation and Scope of a Remarkably Robust Primary Alcohol Protective Group

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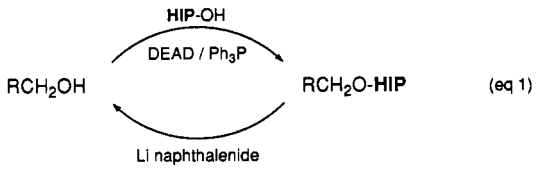
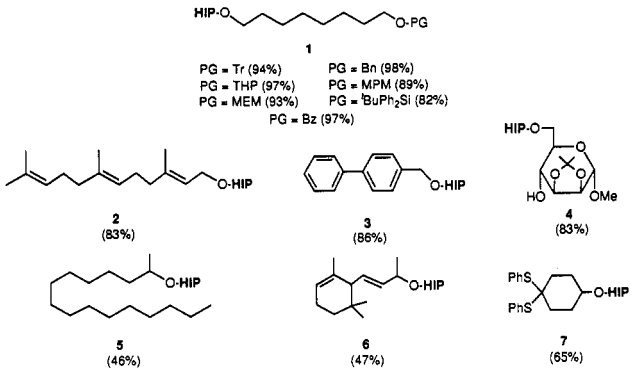
The continuing evolution of organic synthesis and analysis is dependent in many ways on complementary advances[1] in the introduction and manipulation of protective groups (PGs). The design of PGs[2] suitable for contemporary methodology requires a judicious balance of parameters, *inter alia*, availability of the precursor, cost, spectroscopic/physical characteristics, chromatographic properties, efficiency of preparation, stability, and ultimately, selective removal. Herein, we describe the synthetic utility of a novel, primary alcohol PG prepared *via* facile condensation of alcohols with commercial 1,1,1,3,3,3-hexafluoro-2-phenylisopropyl (HIP) alcohol[3] using DEAD and Ph_3P (eq 1). The reaction proceeds at ambient temperature under essentially neutral conditions and represents a special variant of the Mitsunobu reaction[4] in which the fluoro alcohol acts as the proton donor/nucleophile.[5,6] The resultant, achiral HIP ethers are remarkably robust, yet undergo selective cleavage using lithium naphthalenide at low temperature.

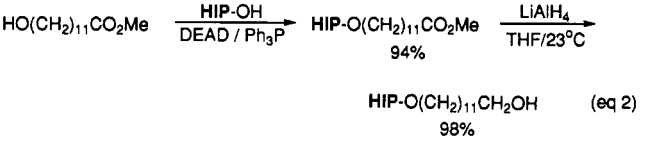


(eq 1)

Primary alcohols react smoothly at ambient temperature in <1 h affording HIP ethers (e.g., **1**) in good to excellent yields. Other alcohol PGs are well tolerated. Dehydration and/or competitive N-alkylation are not observed even for the allylic and benzylic alcohols leading to **2** and **3**. Importantly, etherification is selective for primary alcohols as revealed by the exclusive formation of **4** from methyl 2,3-O-isopropylidene-α-D-mannopyranoside. Nevertheless, HIP ethers can be created from acyclic (e.g., **5** and **6**) and cyclic (e.g., **7**) secondary alcohols, albeit in more modest yields. The principal byproduct in the latter case arises from alcohol dehydration to give the corresponding olefin. Tertiary alcohols, as might be anticipated for a Mitsunobu-type reaction, do not react and are recovered unchanged. The outstanding chemical resistance[7] of the HIP group (*vide infra*) compares favorably with other standardly used ethers such as methyl, benzyl, and trityl. As a consequence of their thermal stability,[7] low polarity, and achiral structure, HIP ethers are amenable to gas chromatography and mass spectrometry. The aromatic chromophore and the cluster of six fluorine atoms also permit detection by sensitive UV and electron capture (EC) techniques, respectively.



HIP ethers are stable over an unusually broad pH range as demonstrated by prolonged exposure to concentrated hydrochloric acid on the one hand and 25 wt % NaOMe in methanol on the other. They also resist many common laboratory oxidants including $K_3Fe(CN)_6$, $(NH_4)_2Ce(NO_3)_6$, SmI_2, pyridinium chlorochromate (PCC), and *N*-bromosuccinimide (NBS). Likewise, nucleophiles (MeLi, N_2H_4), Lewis acids ($BF_3{\cdot}Et_2O$), and various reducing agents typified by Zn/HCl, Na(Hg), and H_2(1 atm)/Pd–C have no effect. A notable exception is $LiAlH_4$ which causes partial (<30%) cleavage of primary HIP ethers under forcing conditions. In practice, however, many hydride reactions, like the ester to alcohol reduction illustrated in eq 2, are significantly faster than HIP cleavage.



(eq 2)

Results from the selective removal of several representative alcohol PGs in the presence of a HIP moiety are summarized in Table 1. The parent alcohols are smoothly regenerated from a trityl ether (entry 1), THP and MEM acetals (entries 2 and 3, respectively), benzylic ethers (entries 4 and 5), silyl ether (entry 6), and benzoate (entry 7) according to literature precedent[2] in good to excellent yields. In contrast, the susceptibility[8] of fluoro ethers to lithium naphthalenide (Li Nphth) can be exploited for the preferential deprotection of HIP ethers in the presence of other PGs. Many common functional groups, *inter alia*, amides, carboxylic acids, unconjugated olefins, and acetylenes, are compatible with the HIP deprotection conditions while others, e.g., esters, epoxides, ketones, and halides, are labile. With stoichiometric Li Nphth, deprotection is rapid (<1 h) even at −78 °C; on a preparative scale, the cleavage is more conveniently

(1) Recent examples: Santoyo-Gonzalez, F.; Garcia-Calvo-Flores, F.; Isac-Garcia, J.; Robles-Diaz, R.; Vargas-Berenguel, A. *Synthesis* **1994**, 97–101. Pirrung, M. C.; Lee, Y. R. *J. Org. Chem.* **1993**, *58*, 6961–6963. Cossy, J.; Albouy, A.; Scheloske, M.; Pardo, D. G. *Tetrahedron Lett.* **1994**, *35*, 1539–1540.

(2) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons, Inc.: New York, 1991.

(3) Available from Aldrich Chem. Co. and PCR, Inc. (Gainesville, FL). Other partially fluorinated alcohols (e.g., 2,2,2-trifluoroethanol) are also suitable participants in the Mitsunobu condensation and, thus, furnish convenient access to a variety of unsymmetric polyfluoro ethers: Falck; J. R.; Yu, J.; Cho, H.-S. *Tetrahedron Lett.*, in press.

(4) Review: Hughes, D. L. *Org. React.* (N.Y.) **1992**, *42*, 335–656.

(5) Ether formation under Mitsunobu conditions usually does not occur, but examples with phenols, enols, and some intramolecular alkyl diols are known: see ref 4, pp 350–354.

(6) Other nontraditional nucleophiles can participate including nitronates and carbon centers: 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.

(7) Hudlicky, M. *Chemistry of Organic Fluorine Compounds: A Laboratory Manual with Comprehensive Literature Coverage*, 2nd ed.; Ellis Horwood Ltd.: New York, 1992.

(8) Sargent, G. D. *J. Am. Chem. Soc.* **1971**, *93*, 5268–5269.

0002-7863/94/1516-8354$04.50/0

Table 1. Selective Removal of HIP Ethers *vs* Other Alcohol Protecting Groups

$$\text{HIP–O(CH}_2)_8\text{OH} \xleftarrow{-PG} \text{HIP–O(CH}_2)_8\text{O–PG} \xrightarrow{\text{Li Nphth}} \text{HO(CH}_2)_8\text{O–PG}$$

	PG removal				HIP removal[a] yield[d] (%)
entry	PG[b]	reactn conditns[c]	time (h)	yield[d] (%)	
1	Tr	$SnCl_2$, CH_2Cl_2	1	89	81
2	THP	*p*-TsOH, MeOH	4	93	89
3	MEM	Me_3SiCl, NaI/CH_3CN[e]	1	88	86
4	Bn	Pd/C, H_2/MeOH	6	91	71
5	MPM	DDQ, CH_2Cl_2/H_2O	1	92	74
6	^{t}BuPh$_2$Si	^{n}Bu$_4$NF, THF	3	95	73
7	Bz	KOH, MeOH	1	97	0[f]

[a] Reaction conditions: lithium naphthalenide (excess), THF, −78 °C (see general procedure). [b] Tr = Ph_3C; THP = tetrahydropyranyl; Bn = $PhCH_2$; MPM = 4-$MeOC_6H_4CH_2$; MEM = $CH_3OCH_2CH_2OCH_2$; Bz = PhC(O). [c] Conducted at ambient temperature. [d] Isolated yield of chromatographyically and spectrally pure material. [e] Conducted at −20 °C. [f] Bz and HIP are both cleaved to give the diol in good yield.

conducted using Li sand and a catalytic amount of naphthalene, although the reaction requires more time to reach completion.

The general procedure for the preparation of HIP ethers is as follows. A solution of DEAD (1.5 mmol) in anhydrous benzene (2 mL) was added dropwise to a stirring, room temperature solution of alcohol (1.0 mmol), HIP alcohol (1.2 mmol), and Ph_3P (1.5 mmol) in the same solvent (10 mL). After 1–2 h, the reaction was complete and all volatiles were removed *in vacuo*. Chromatographic purification on silica gel afforded the HIP ether in 84–99% yields for primary alcohols and 45–70% yields for secondary alcohols.

The general procedure for Li Nphth cleavage is as follows: Naphthalene (0.1 mmol) was added through an argon blanket to a stirring suspension of Li sand (30% in mineral oil, 1.0 mmol) in anhydrous THF (3 mL). After 5 min, the deep blue reaction mixture was cooled to −78 °C and a solution of HIP ether (0.2 mmol) in THF (2 mL) was added dropwise. Complete consumption of starting material required 5–10 h, but could be accelerated by using more naphthalene. The liberated alcohol was isolated by quenching with saturated NH_4Cl solution, extraction with an organic solvent, and chromatographic purification on silica gel.

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Supplementary Material Available: HRMS and $^1H/^{13}C$ NMR spectra for **4** and HIP ethers in Table 1 (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.