Tetrahydrofuranylation of Alcohols Using Hypervalent Iodine Reagents

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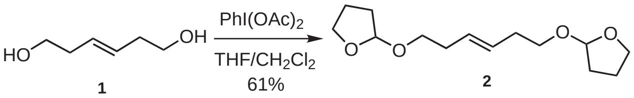
Received 1 July 2004

To the memory of Anne Ghosez-Giese.

Abstract: Alcohols are converted to their corresponding 2-tetrahydrofuranyl ethers using (diacetoxyiodo)benzene in THF. Reactions are carried out under reflux, or, more effectively, under microwave irradiation. Yields up to 81% are reported without the use of chlorinated solvents.

Key words: hypervalent iodine, *bis*-THF-ether adduct, oxidations, protecting groups, microwave

For a number of years, we have been interested in the synthesis and reactions of hypervalent iodine reagents.[1] Recently, in an investigation of the cyclization of hydroxyalkene **1** using hypervalent iodine compounds, a fortuitous observation led us to discover a further use for iodine(III) reagents. Thus, reaction of diol **1**, with (diacetoxyiodo)benzene at 40 °C, in THF–CH_2Cl_2 gave a single product in 61% yield. NMR and mass spectral analysis indicated this compound to be the *bis*-THF-ether adduct **2** (Scheme 1).



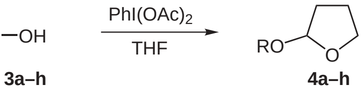
Scheme 1 Reaction of 3-hexen-1,6-diol with $PhI(OAc)_2$

Subsequent investigations into the generality, and optimizations of this discovery are presented herein.

A survey of the literature shows a wide variety of methods for the formation of 2-tetrahydrofuranyl ethers that spans five decades.[2] Recent methods center on the use of one electron oxidants, such as peroxodisulfates,[2h] cerium(IV) reagents,[2g] $CrCl_2$,[2k] or most recently peroxy-λ^3-iodanes,[2m] to activate tetrahydrofuran. Recent work by Ochiai has demonstrated that 1-*tert*-butylperoxy-1,2-benziodoxol-3-1*H*-one, alone or coupled with carbon tetrachloride, can yield tetrahydrofuranylated alcohols.[2m]

Many of these methods share a significant disadvantage as well; the requirement of carbon tetrachloride or similar perhalomethane to propagate the reaction or to serve as a chlorine source in the in situ formation of 2-chlorotetrahydrofuran, the reactive species in these tetrahydrofuranylations of alcohols. As carbon tetrachloride and bromotrichloromethane are almost completely banned from use, even in research, these sometimes superior reactions will be inaccessible in the near future.

Iodine(III) compounds have been known for some time to be excellent oxidants, and reagents for radical reactions.[3] There has been little discussion of there potential as reagents for the formation of protecting groups.

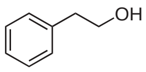
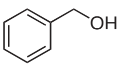
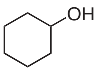
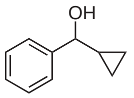
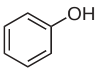
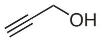
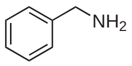


Scheme 2 Tetrahydrofuranylation of alcohols using $PhI(OAc)_2$

2-Tetrahydrofuranyl ethers **4a**–**h** (Scheme 2) can be prepared in reasonable yields by the reaction of one equivalent of (diacetoxy)iodobenzene, alcohol **3a**–**h**, and tetrahydrofuran as reagent and solvent at elevated temperatures. Thus, heating THF solutions of the desired alcohol and (diacetoxy)iodobenzene in a sealed tube at 80 °C gave modest yields of the desired 2-tetrahydrofuranylated product. Although we never detected *bis*-tetrahydrofuran as a side product, a radical reaction mechanism cannot be completely excluded.[2h,l] The formation of the tetrahydrofuranyl cation by oxidation with $PhI(OAc)_2$ is most likely to be the key step in this reaction. Marked increases in yield in some cases could be obtained by the use of a microwave reactor. Even better yields could be obtained, in some cases, by irradiating a solution of the three components with microwaves under simultaneous cooling conditions[4] for 1–3 hours. In all cases, reaction times were greatly reduced using microwave irradiation over conventional heating. Simple aliphatic primary alcohols like decanol and octanol gave good to excellent yields (Table 1, entries 1, 2) with only a trace of alcohol oxidation to the corresponding aldehydes. Aliphatic secondary alcohols (Table 1, entry 5) gave still moderate yields with no evidence of oxidation. Benzyl alcohols (Table 1, entry 4) gave good yields, but suffered from increased oxidation to the corresponding benzaldehyde (up to 20%). Tertiary alcohols proved unreactive under both thermal and microwave conditions. Forcing conditions (higher microwave power and/or higher temperatures) resulted in decomposition and gave a variety of elimination products. Yields of

SYNLETT 2004, No. 13, pp 2291–2294
Advanced online publication: 08.09.2004
DOI: 10.1055/s-2004-832810; Art ID: D17104ST

Table 1 Reactions under Thermal and Microwave Conditions

		Concentration 2.0 M, yield of THF-ether **4a–h** (reaction time)		Concentration 0.8 M yield of THF-ether, **4a–h** (reaction time)	
Entry	Substrates	Thermal[a]	Microwave[b]	Thermal[a]	Microwave[b]
1	*n*-Octanol, **3a**	60% (24 h)	63% (1 h)	68% (60 h)	68% (0.5 h)
2	*n*-Decanol, **3b**	56% (72 h)	81% (1 h)	61% (24 h)	61% (1 h)
3	 **3c**	56% (92 h)	34% (4 h)	55% (92 h)	38% (2.5 h)
4[c]	 **3d**	52% (96 h)	76% (1 h)	50% (24 h)	63%(1.5 h)
5	 **3e**	69% (72 h)	52% (3 h)	55% (24 h)	59% (3 h)
6[d]	 **3f**	Mixture (24 h)	10% (3 h)	35% (92 h)	39% (2.5 h)
7	 **3g**	Polymer + **3g** (15 h)	Polymer (1 h)		Polymer (1 h)
8	 **3h**			4% (96 h)	7% (3 h)
9	 **3i**			27% PhCHO + **3i**	

[a] Thermal conditions: 2.0 mmol each of iodine reagent and alcohol, with THF in a sealed microwave tube at 75–90 °C, for allotted time (in parentheses).

[b] Microwave conditions: 2.0 mmol each of iodine reagent and alcohol, with THF in a sealed microwave tube in microwave reactor set to 100 °C (100 W) with air cooling (actual temperature 83–87 °C), for allotted time (in parentheses).

[c] 15–20% Benzaldehyde was isolated as well.

[d] 15% Ketone was isolated.

reactions with cinnamyl or propargyl alcohol were too low to be of practical use. Starting material and oxidation products were recovered.

The effect of concentration on the tetrahydrofuranylation was also investigated. An increase in concentration (decrease in equivalents of THF) in the reactions gave mixed results. In some cases higher yields of the tetrahydrofuranylated products were observed (Table 1, entries 2, 4, 5), especially evident in the microwave reactions.

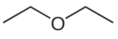
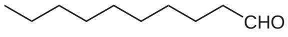
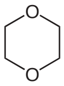
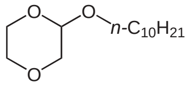
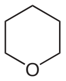
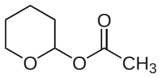
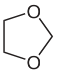
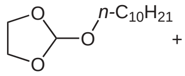
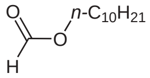
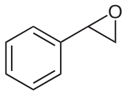
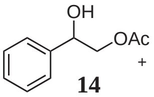
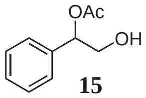
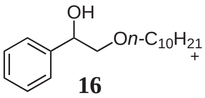
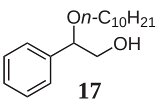
The reaction of phenol gave an insoluble polymer upon reaction with the iodine(III) reagent, presumably via an oxidation and self-condensation of the phenolic ring. The work of Kita[5] has shown that phenolic coupling with hypervalent iodine reagents is a powerful tool in organic synthesis.

Benzylamine as the nucleophile was attempted under microwave conditions. Witulski reported the reaction of propargylic amines with aryl iodonium salts in THF gave good yields of the tetrahydrofuranylated amine product.[6] Likewise, Varvoglis had reported that the corresponding thermal reaction of aliphatic amines with $PhI(OAc)_2$ gave a mixture of products.[7] The microwave reaction was performed with THF and benzaldehyde was obtained in a 27% yield. Nicolaou and coworkers observed similar oxidative behavior using IBX, an iodine(V) reagent,[8] and Moriarty showed that secondary amines could be oxidized to the corresponding imines.[9]

Reaction of THF and *n*-octanol were also performed using other iodine(III) reagents under the optimized microwave and thermal conditions. Both hydroxy(tosyloxy)iodobenzene and bis(trifluoroacetoxy)iodobenzene failed to give appreciable yields (<15%) of the tetrahydrofuranylated alcohol, but rather gave either starting material or an intractable mixture of degradation–oxidation products.

An investigation was carried out into the scope of these reaction conditions by reacting $PhI(OAc)_2$ and decanol in the presence of a number of other ethers, using the optimized microwave and thermal methods as shown in

Table 2 Reaction of Ethers with $PhI(OAc)_2$ and Decanol under Microwave and Thermal Conditions[10]

Entry	Ether	Product(s)	Yield (%) microwave conditions[a]	Yield (%) thermal conditions[b]
1	 **5**	 **6**	<10	–
2	 **7**	 **8**	10	8
3	 **9**	 **10**	**10** (17) + **6** (3)	38
4	 **11**	 **12** +  **13**	0, **11** recovered	**12** (23), **13** (11)
5	 **14**	**6** +  **14** +  **15**  **16** +  **17**	**6** (40)[c]	**14** (13), **15** (3), **16** (6), **17** (3), + Polymers

[a] With air cooling (100 W, actual temperature 83–87 °C), for 4 h.

[b] Thermal conditions: 2.0 mmol each of $PhI(OAc)_2$ and alcohol, with cyclic ether in a sealed microwave tube at 75–90 °C, for 24 h.

[c] When CH_2Cl_2 was used as a co-solvent, under microwave conditions, a 2:1 mixture of **14** and **15** was isolated in 88% yield.

Table 2. Reaction of decanol and $PhI(OAc)_2$ with diethyl ether gave only oxidation of decanol, and no acetal product. Reaction of 1,4-dioxane under microwave conditions gave only 10% of the desired acetal (Table 2, entry 2), while thermal reaction conditions gave only 8%. Reaction of tetrahydropyran under identical reaction conditions (microwave and thermal) gave 17% and 38%, respectively, of the tetrahydropyranyl acetate **10** along with a small amount (3%) of decanal (Table 2, entry 3). Of equal interest was the reaction of 1,3-dioxolane under these reaction conditions. It was hoped that oxidation of the formyl methylene and reaction with the alcohol would access the orthoester. While microwave reaction gave only starting material, the thermal reaction gave two major products; the desired orthoester **12** and formyl decanoate **13** (Table 2, entry 4) in low yields.

Finally, reaction of styrene oxide under microwave conditions (Table 2, entry 5) gave large quantities of unreacted $PhI(OAc)_2$ and oxidation of decanol. The corresponding thermal reaction gave a mixture of six compounds, **14–17**, resulting from epoxide opening by either acetate or decanol, in low yield and two others that appear to be polymeric in nature. For solubility reasons, and for comparison, we performed the microwave reaction with dichloromethane as a co-solvent, and we obtained an 88% yield of the acetylated alcohols, **14** and **15**, as a 2:1 mixture.

In summary, we have revealed a new procedure for the tetrahydrofuranylation of simple alcohols using $PhI(OAc)_2$, and THF as both solvent and reagent. Significant rate enhancements can be seen, in some cases, when the reactions are carried out in a microwave reactor.

Acknowledgment

We thank the Royal Society for providing a Royal Society USA Fellowship for ANF during his sabbatical year (2003-2004). We acknowledge the Royal Society, The National Science Foundation (INT-0209956), and the Donors of the American Chemical Society Petroleum Research Fund, for funding this collaboration as well as support by the EPSRC (GR/S 25456 and GR/S 73105).

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(10) **Microwave Tetrahydrofuranylation.** $PhI(OAc)_2$ (644 mg, 2.0 mmol), THF (2.50 mL) and decanol (0.38 mL, 2.0 mmol) were placed in a microwave tube, with a magnetic stirrer and sealed. The tube was placed in a CEM Discovery Microwave reactor and heated (at 100 W) to 100 °C over 5 min, then maintained at 100 °C for 1 h. Following a 30 min cool time, the tube was removed and the contents purified directly by flash chromatography, using 8:1 petroleum ether–Et_2O. The required fractions were concentrated under reduced pressure to afford a clear, colorless liquid (369 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.79$ (t, 3 H), 1.10–1.30 (m, 14 H), 1.47 (pent., 2 H), 1.65–1.97 (m, 4 H), 3.28, 3.57, 3.79, 5.03. ^{13}C NMR (100MHz, $CDCl_3$): $\delta = 14.4$, 23.0, 23.9, 26.56, 29.62, 29.68, 29.8, 29.9, 30.1, 32.3, 32.7, 67.0, 67.6, 104.0. MS (EI, 70 eV): m/z (%) = 227 (5) [$M - H^+$], 211 (7), 141 (72), 71 (100), 57 (9), 43 (28), 41 (30).
Thermal Tetrahydrofuranylation. $PhI(OAc)_2$ (322 mg, 1.0 mmol), THF (1.25 mL) and decanol (0.19 mL, 1.0 mmol) were placed in a microwave tube, with a magnetic stirrer and sealed. The tube was placed in an oil bath at 85 °C, for 24 h. The THF was removed under reduced pressure, and the product purified by flash chromatography, using 8:1 petroleum ether–Et_2O (145 mg, 61%).