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Alkynyliodonium Salts in Organic Synthesis. Preparation of 2-Substituted-3-*p*-toluenesulfonyldihydrofurans from 1-Hydroxybut-3-ynyliodonium Ethers via a Formal Stevens Shift of a Carbon Group

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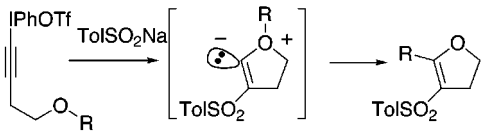
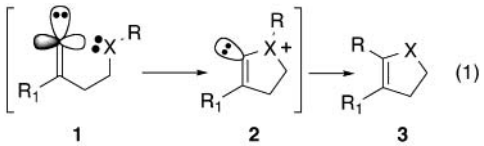
ABSTRACT



***p*-Toluenesulfinate addition to 1-hydroxybut-3-ynyliodonium ethers triggers a sequence of reactions which ultimately delivers 2-substituted-3-*p*-toluenesulfonyldihydrofuran products along with 3-*p*-toluenesulfonyldihydrofuran as a major byproduct. A putative 1,2-alkyl shift within an unsaturated oxonium ylide (Stevens rearrangement) accounts for the oxygen-to-carbon transfer of the alkyl group.**

The utility of alkynyliodonium salts in organic synthesis stems largely from their role as alkylidene carbene precursors upon combination with select nucleophiles.[1] These reactive monovalent carbenes participate in a range of C−C, C−H, and C−X bond-forming processes which all appear to originate with an interaction between the empty p orbital at the terminus of the electrophilic carbene and a proximate source of electron density (e.g., C−H, C═C, or X−H bond).[2] In contrast, the formal combination of an alkylidene carbene with a heteroatom lone pair (cf. **1** → **2**, eq 1) has been much



(1)

less thoroughly investigated, and productive reactions have heretofore been limited to cases where R = H or SiR′$_3$.[3] In these instances, dihydrofuran derivative **3** is produced, presumably via Stevens rearrangement[4] (1,2 R shift) within the oxonium ylide **2**. Attempts at detecting a similar shift with a carbon group (R = allyl or benzyl) by Kim et al. were frustrated by intervention of uncharacterized reaction channels which diverted the ylide intermediate.[3a]

A recent observation of alkylidene carbene addition to the lone pair of a carbamate nitrogen suggested that this process may be more general than otherwise suspected[5] and that by proper choice of the migrating group R in **1**, efficient Stevens rearrangement of a carbon-based group might be realized. In this vein, we report the successful conversion of the simple alkynyliodonium salts **4** into the 2,3-disubstituted dihydrofuran products **7** by treatment with the mild nucleophile *p*-toluenesulfinate (eq 2). These transformations presumably

(1) (a) Stang, P. J.; Zhdankin, V. V. *Tetrahedron* **1998**, *54*, 10927. (b) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179.
(2) Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164.
(3) (a) Kim, S.; Cho, C. M. *Tetrahedron Lett.* **1995**, *36*, 4845. (b) Ito, Y.; Aoyama, T.; Shioiri, T. *Synlett* **1997**, 1163. (c) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 461. (d) see also Sueda, T.; Nagaoka, T.; Goto, S.; Ochiai, M. *J. Am. Chem. Soc.* **1996**, *118*, 10141.
(4) Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford 1991; Vol. 3, Chapter 3.10.
(5) Feldman, K. S.; Mingo, P. A.; Hawkins, P. C. D. *Heterocycles* **1999**, *51*, 1283.

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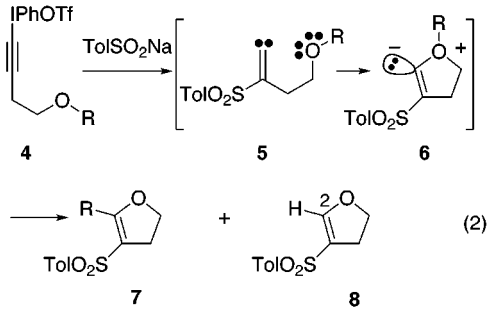
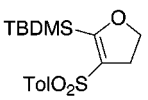
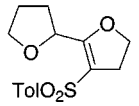
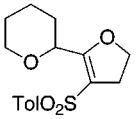
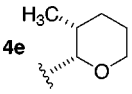
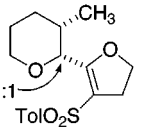
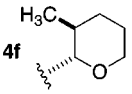
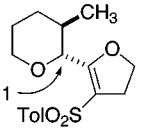
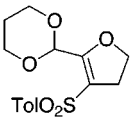


pass through a formal Stevens 1,2-shift of R within the ylide **6** to fashion the new C−C bond in **7**. Variable but significant quantities of the proton-trapping product **8** are formed as well, and formation of this compound constitutes the major yield-limiting competition in the sequence. The choice of sulfinate as a nucleophile was predicated on a desire to prepare an enol ether product **3** whose alkene would not be sensitive to hydrolysis upon isolation/chromatography. In principle, the range of nucleophiles with reported utility in converting an alkynyliodonium salt into the derived carbene (sulfonamide anion, azide, β-dicarbonyl enolate, etc.)[1] may be applicable to this transformation as well.

A series of alkynyliodonium salts **4a**−**4g** was prepared and examined in this dihydrofuran-forming reaction, Table 1. These salts were readily available by treatment of the corresponding alkynyltributylstannanes with Stang's reagent, PhI(CN)OTf. The thermal lability of these species required that temperatures did not exceed −30 °C during their preparation and handling. Optimization studies with substrates **4a** and **4d** spanned a range of experimental variables, including order and rate of addition, concentration (0.15−0.30 M in iodonium salt), temperature (room temperature → refluxing solvent), and solvents (CH_2Cl_2, $ClCH_2CH_2Cl$, THF, DME, t-BuOMe, DMF), to maximize production of the dihydrofuran products **7a** and **7d**, respectively. Eventually, a procedure by which a chilled (−42 °C) THF solution of the alkynyliodonium salt **4d** was rapidly cannulated into refluxing THF containing a suspension of 1.3 equiv of anhydrous sodium *p*-toluenesulfinate (final concentration ∼ 0.15 M alkynyliodonium salt) was found to provide the desired cyclized/rearranged dihydrofuran product **7d** in optimal yield. Further experimental details can be found in the Supporting Information.

Verification of Kim's observations that silicon migrates effectively (entry a) while benzyl does not (entry b) provided a baseline for subsequent studies. Better carbon migration results are obtained with the tetrahydrofuran and tetrahydropyran series, entries c−f. With both the simple unsubstituted rings (entries c and d, respectively), the desired 2-tetrahydrofuranyl- and 2-tetrahydropyranyldihydrofurans are formed in moderate yields. The formal Stevens rearrangement appears to proceed with reasonable levels of stereochemical fidelity in the tetrahydropyran series, entries e and f. Each pure diastereomer of the 3-methyl-substituted substrates **4e** and **4f** provides a diastereomeric mixture of 2-dihydrofuranyltetrahydropyran products that strongly favors retention of the stereochemical relationship present in the starting material. The ratios of diastereomers were determined

Table 1. 2-Substituted-3-*p*-toluenesulfonyldihydrofuran Products **7** Prepared from Alkynyliodonium Salts **4** in THF at Reflux

entry		R		7[a] (% yield)	8 (%)
a	**4a**	TBDMS[b]	**7a** (65)		----
b	**4b**	Bn	---------		19
c	**4c**		**7c** (35)		25
d	**4d**		**7d** (41)		27
e	**4e**		**7e** (41)	 **7e:7f = 8.5:1**	16
f	**4f**		**7f** (43)	 **7f:7e = 10:1**	16
g	**4g**		**7g** (68)		----

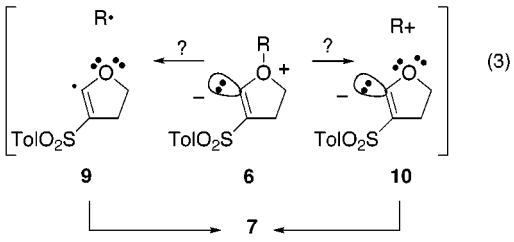
a All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR, LRMS and combustion analysis. See Supporting Information for details. *b* CH_2Cl_2 at room temperature

by integration of diagnostic signals in the ^{1}H NMR spectra. The stereochemical assignments were predicated upon analysis of the coupling constants between protons on the stereogenic centers (**7e**, $J_{1,2}$ = 3.6 Hz; **7f**, $J_{1,2}$ = 10.0 Hz). Treatment of orthoester-containing substrate **4g** with *p*-toluenesulfinate provided acetal **7g** in superior yield, and none of the protonated dihydrofuran **8** was detected. This observation draws attention to the possible role that the C(3) THP proton (H in **4d**) plays in the formation of the dihydrofuran byproduct **8**.

The mechanistic course of this transformation is believed to proceed through the oxonium ylide **6** en route to dihydrofuran product **7**. Evidence that has been interpreted as supporting either homolytic or heterolytic scission of the C−O bond within trivalent oxonium ylides has been recorded,[6] but no mechanistic investigations that factor in

(6) (a) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062. (b) Eberlein, J. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479. (c) Doyle, M. P.; Griffin, J. H.; Chinn, M. S.; van Leusen, D. *J. Org. Chem.* **1984**, *49*, 1917.

the influence of a divalent carbanion (cf. **6**) in the Stevens rearrangement have been reported. A priori, two limiting mechanisms proceeding through either homolytic C−O cleavage (e.g., **9**) or heterolytic C−O cleavage (e.g. **10**) can be envisioned (eq 3). On the basis of the limited structure/



(3)

reactivity data gleaned from Table 1, it is tempting to suggest that the heterolytic scission pathway is favored in these rearrangements. Thus, substituents R in **6** which were anticipated to promote homolytic cleavage perform poorly (i.e., benzyl, allyl, and *p*-methoxybenzyl (not shown, **7** not formed), while, in contrast, substrates whose substituent R has a documented capacity to stabilize cationic character (silyl, α-THF, α-THP) fare much better. Further studies to probe this point are planned, as are experiments designed to illuminate allied issues regarding the intra- vs intermolecular nature of the formal 1,2-shift and the source of the proton at C(2) in **8**.

In summary, a novel application of arylalkynyliodonium salts bearing terminal ether functionality to the synthesis of dihydrofurans is reported. This sequence likely involves a sequence of events which generates, in turn, reactive intermediate alkylidene carbenes and oxonium ylides. In essence, this transformation converts an easy-to-make O−R bond in the alkynyliodonium salt precursor into a more difficult-to-make C−C bond in the product dihydrofuran. Efforts to expand the scope and define the limitations of this reaction are in progress, and results will be reported in due course.

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Supporting Information Available: A representative experimental procedure for the formation of **7d** and characterization data (^{1}H NMR, ^{13}C NMR, IR, LRMS, and combustion analysis) for **7a**, **7c**−**g**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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