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Access to Cis-2,5-Disubstituted Iodovinyltetrahydrofurans via the Cyclization of γ-Silyloxyallenes Using N-Iodosuccinimide

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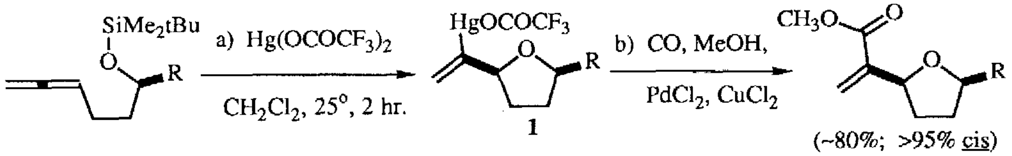
Abstract: *Treatment of γ-(tert-butyldimethylsiloxy)- or γ-(trimethylsiloxy)allenes bearing various groups at the ether carbon with N-iodosuccinimide resulted in the formation of iodocyclization products, 1-iodo-1-(tetrahydrofuran-2'-yl)ethenes, in good yields and with high selectivity for the cis diastereomer.*

In earlier reports, we described an efficient synthetic process for producing cis-2,5-disubstituted tetrahydrofurans bearing an acrylate moiety via the intramolecular oxymercuration of γ-silyloxyallenes, to form cis 1-(tetrahydrofuran-2'-yl)ethenylmercury intermediates (1), followed by a palladium(II)-mediated methoxy-carbonylation, as shown in equation 1.[1] While this methodology for forming substituted "furanylacrylates" is applicable to numerous synthetic problems, including an ongoing project aimed at the synthesis of the antibiotic pamamycin-607,[2] further research in our laboratory has indicated that the intermediates **1** do not undergo many of the coupling reactions which have been previously shown to be characteristic of vinylmercuric compounds.[3] Instead, decomposition of the starting material to intractable product mixtures or recovery of the vinylmercuric compound is observed.[4]



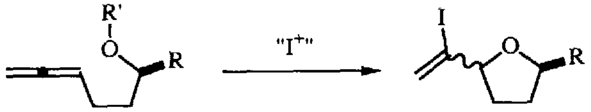
(1)

The disappointing results from our attempts to use the vinylmercury intermediates **1** for synthetic objectives other than methoxycarbonylation has led us to investigate the iodocyclization of γ-silyloxyallenes to form 1-iodo-1-(tetrahydrofuran-2'-yl)ethenes (**2**, equation 2) with the hope that such cyclizations would proceed with cis selectivity and that the resulting vinyl iodide products **2** would prove to be more versatile as synthetic intermediates than the vinylmercurials **1**. The diminished toxicity hazard associated with forming and handling vinyliodide intermediates instead of vinylmercury intermediates was a further incentive for these investigations. This communication describes some of our preliminary results.

The iodocyclization of γ-benzyloxy- or γ-silyloxyalkenes using iodine results in the selective formation of cis-tetrahydrofurans bearing an iodoalkyl group at the newly formed stereogenic carbon of the tetrahydrofuran ring, thus providing a precedent for our studies of allenes.[5] In addition, Friesen and coworkers have investigated the intramolecular amidoiodinations of α-allenic alcohol carbamates, also using iodine, to form 4-iodoethenyloxazolidinones.[6] To our knowledge, the intramolecular iodocyclizations of hydroxyallenes or their ether derivatives have not been reported up to now.[7]

Our results are indicated in Table 1. When a series of variously substituted γ-hydroxyallenes[8] were treated with iodine in the presence of potassium carbonate or sodium bicarbonate in dichloromethane, the iodovinyltetrahydrofurans were produced in variable yields as ~50:50 mixtures of cis/trans diastereomers (Table 1, entries 1-6). In an attempt to induce cis-selectivity via the use of cleavable ether derivatives, we treated the 2,6-dichloro-

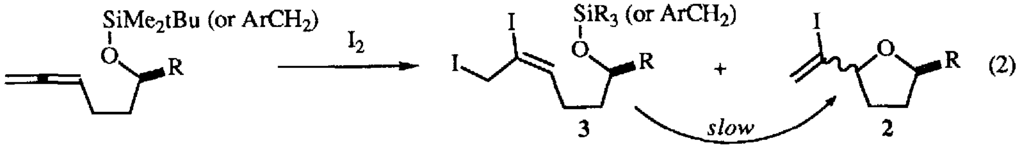
Table 1. Iodocyclizations of γ-Hydroxyallenes and Derivatives.



Entry	R	R'	Conditions[a,b]	Yield[c]	Cis : Trans[d]
1	CH_3	H	I_2	73%	42 : 58
2	CH_2CH_3	H	I_2	70%	37 : 63
3	CH_2CH_2OMPM[e]	H	I_2	57%	50 : 50
4	anti-$CH(CH_3)COODBMP$[f]	H	I_2	55%	46 : 54
5	$CH_2COODBMP$[f]	H	I_2	55%	52 : 48
6	$CH_2COOtBu$	H	I_2	43%	40 : 60
7	CH_3	DCB[g]	I_2	50%	62 : 37
8	CH_3	$SiPh_2tBu$	I_2	54%	58 : 42
9	CH_3	$SiMe_2tBu$	I_2	55%	65 : 35
10	CH_3CH_2	$SiMe_2tBu$	I_2	75%	40 : 60
11	CH_2CH_2OMPM[e]	$SiMe_2tBu$	I_2	51%	48 : 52
12	anti-$CH(CH_3)COODBMP$[f]	$SiMe_2tBu$	I_2	72%	44 : 56
13	$CH_2COODBMP$[f]	$SiMe_2tBu$	I_2	43%	61 : 39
14	CH_3	$SiMe_3$	NIS	61%	86 : 14
15	CH_3	$SiMe_2tBu$	NIS	97%	88 : 12
16	CH_2CH_3	$SiMe_3$	NIS	88%	93 : 7
17	$CH(CH_3)_2$	$SiMe_3$	NIS	95%	96 : 4
18	CH_2CH_2OMPM[e]	$SiMe_3$	NIS	93%	92 : 8
19	anti-$CH(CH_3)COODBMP$[f]	$SiMe_3$	NIS	87%	>98:<2[h]
20	$CH_2COODBMP$[f]	$SiMe_3$	NIS	93%	98: 2
21	$CH_2COOtBu$	$SiMe_3$	NIS	90%	88: 12

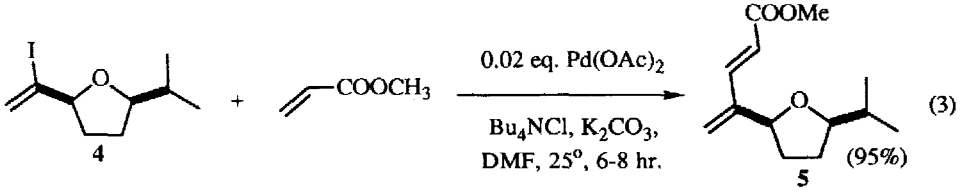
[a] "I_2" = 1 equivalent of iodine, excess sodium bicarbonate, acetonitrile, 0° C., 2-5 hr. [b] "NIS" = reaction conditions described in reference 12. [c] Yield of both diastereomers together following chromatographic purification (reference 12). [d] Measured by integration of ^{1}H-NMR signals (reference 9); error is ca.±5. [e] MPM = para-methoxyphenyl-methyl. [f] DBMP = 2,6-di-tert-butyl-4-methoxyphenyl. [g] DCB = 2,6-dichlorobenzyl. [h] The *trans* isomer could not be detected in the crude product mixture.

benzyl ether derivative[8] (the type of ether which Bartlett found to allow for the highest stereoselection in the iodocyclizations of alkenes[5]) of 5,6-heptadien-2-ol with iodine. This resulted in a mixture of cyclized products enriched, to some extent, in the cis isomer (Table 1, entry 7).[9] Changing the ether group (with various substrates) to tert-butyldiphenylsilyl, tert-butyldimethylsilyl, or trimethylsilyl ethers[8] resulted in varying outcomes (Table 1, entries 8-13), none of which represented good stereoselectivity. We eventually discerned that the initial exposure of these ether derivatives to iodine resulted in the production of a mixture of the cyclized products (**2**) plus significant amounts (~20-30%) of the diodides **3** which, upon standing, slowly cyclized to **2** (equation 2).[10] Therefore, it appears that the iodocyclization reaction of γ-alkoxy- or γ-silyloxyallenes with iodine proceeds, entirely or in part, via the diiodide **3** which is then converted into **2** by an S_N2'-type step. This process, which Friesen suggested to be operative in his iodocyclizations,[6] was found to lack stereoselectivity in our system. It is interesting that the iodocyclizations of aminoallenes using iodine reported by Gallagher and coworkers also proceeded via diiodide intermediates.[7] Diiodide derivatives of allenes are known.[11]



Because of the poor stereoselectivity of the iodocyclizations of our γ-hydroxyallene derivatives when processed via a diiodide intermediate, we decided to investigate N-iodosuccinimide (NIS) as an alternative source of "I^+" because it would be unaccompanied by as strong a nucleophile as iodide. As indicated in Table 1 (entries 14-21), treatment of γ-(tert-butyldimethylsilyl)- or γ-trimethylsilylallenes with NIS results in the formation of 1-(tetrahydrofuran-2'-yl)ethenyl iodides in good to excellent yields and with high cis selectivity. The examples listed in Table 1 indicate the versatility of this methodology and the expected correspondence between the cis:trans product ratio and the bulkiness of the group attached to the carbinol carbon (e.g. Table 1, entries 14 vs. 16 vs. 17).[5] Optimum results were obtained when a 4:1 (v:v) dichloromethane:tetrahydrofuran solvent system (chosen on the basis of its ability to dissolve NIS) was employed.[12] As indicated in Table 1, the cheaper trimethylsilyl ether derivatives were used for the "optimized" cyclizations. One example suggests that the tert-butyldimethylsilyl ether derivative may result in a higher yielding transformation (Table 1, entries 14 vs. 15), but the volatility of the particular product obtained in that case may cause significant variations in the observed yields from one "run" to another.

In summary, a mild, high-yielding, and cis-selective synthetic route to 1-(tetrahydrofuran-2'-yl)ethenyl iodides (**2**) has been developed. As a testimony to the synthetic versatility of these substituted vinyl iodides, especially in contrast to their vinylmercury counterparts **1**, the Heck reaction between the cis tetrahydrofuranylethenyl iodide **4** and methyl acrylate produced the diene **5** in a highly efficient manner (equation 3).[13] Details of our investigations of this and other useful transformations of the vinyl iodides **2** will be reported in the future.



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References and Notes

1. a) Walkup, R.D.; Park, G. *Tetrahedron Lett.* **1987**, *28* , 1023-1026; b) Walkup, R.D.; Park, G. *J. Am. Chem. Soc.* **1990**, *112* , 1597-1603; **1990**, *112* , 5388.

2. Walkup, R.D.; Park, G. *Tetrahedron Lett.* **1988**, *29* , 5505-5508.

3. Larock, R.C. *Organomercury Compounds in Organic Synthesis* ; Springer-Verlag: New York. 1985; chapter VII.

4. One partial success was the coupling of intermediates **1** to allylic halides to produce 2-(tetrahydrofuran-2'-yl)-1,4-pentadienes in low yields: Walkup, R.D.; Guan, L. *Synthetic Commun.* **1992**, *22* , in press.

5. For overviews, see Bartlett, P.A. Olefin Cyclization Processes That Form Carbon-Heteroatom Bonds. In *Asymmetric Synthesis;* Morrison, J.D., Ed.; Academic Press: New York, 1984; pp. 411-454; Reitz, A.B.; Nortley, S.O.; Maryanoff, B.E.; Liotta, D.; Monahan, R. *J. Org. Chem.* **1987**, *52* , 4191-4202; Cardillo, G., Orena, M. *Tetrahedron* **1990**, *46* , 3321-3408; Harding, K.E., Tiner, T.H. Electrophilic Heteroatom Cyclizations. In *Comprehensive Organic Synthesis;* Trost, B.M., Fleming, I., Eds., Vol. 4; Pergamon Press: New York, 1991; pp. 363-421.

6. Friesen, R.W.; Kolaczewska, A.E. *J. Org. Chem.* **1991**, *56* , 4888-4895 and references cited therein.

7. For a report on iodocyclizations of ω-amidoallenes to form nitrogen heterocycles, see Shaw, R.; Anderson, M.; Gallagher, T. *SynLett* **1990**, 584-586.

8. The γ-hydroxyallenes were prepared by the addition of Grignard reagents (CH_3MgCl, CH_3CH_2MgBr, $(CH_3)_2CHMgBr$) or lithium enolates (derived from LDA and $CH_3CH_2COODBMP$, $CH_3COODBMP$, $CH_3COOtBu$) to 4,5-hexadienal. The R = CH_2CH_2OMPM γ-hydroxyallene was prepared by $LiAlH_4$ reduction of the β-hydroxy tert-butyl ester followed by alkylation using MPMCl. The ether derivatives were prepared using standard alkylation or silylation methodology. See references 1 and 2 for relevant details. Detailed information about the experimental procedures, including isolation and characterization data, are available from the authors upon request.

9. The assignments of the cis and trans geometries were made using ^{1}H-NMR, based on the anticipated upfield chemical shifts of the ring methine hydrogens in the cis isomer relative to the trans isomer. Trends in the observed NMR signals for the iodoethenyl and alkyl sidechains (cis ⇒ downfield, trans ⇒ upfield) were also observed. Diagnostic ^{1}H-NMR signals ($CDCl_3$, TMS standard) for the iodoethenyltetrahydrofuran products: Cis isomers: δ 6.43-6.45 (1H, t, $J\approx1$ cps; vinyl H); 5.81 (1H, d, $J\approx1$ cps; vinyl H); 4.13-4.18 (1H, m; allylic H). Trans isomers: δ 6.37-6.43 (1H, t, $J\approx1$ cps; vinyl H); 5.7 (1H, d, $J\approx1$ cps; vinyl H); 4.27-4.34 (1H, m; allylic H). The cis/trans ratios were determined by measuring the relative integrations of the ^{1}H-NMR signals for the vinyl hydrogens as they appeared in the NMR spectrum of the crude product mixtures. In some cases the cis and trans isomers were separated by HPLC. More detailed experimental data are available from the authors upon request.

10. The diiodide byproducts were formed as mixtures of E/Z isomers. Diagnostic ^{1}H-NMR signals ($CDCl_3$, TMS standard): δ 6.0 (t, $J\approx7$ cps; vinyl H for Z isomer); 6.2 (t, $J\approx7$ cps; vinyl H for E isomer); 4.3-4.4 (2H, s; CH_2I). In some cases, the diiodide byproducts were isolated by chromatography. In most cases, the presence of the diiodide was deduced by ^{1}H-NMR analyses of the crude product mixtures.

11. Smadja, W. *Chem. Rev.* **1983**, *83* , 263-320.

12. General Procedure for the NIS-Mediated Iodocyclizations of γ-Silyloxyallenes. (In all cases, the NIS was prepared in situ as described). Equimolar amounts of N-chlorosuccinimide and sodium iodide were dissolved separately in dry acetone (0.3 M solutions of each), then mixed together and stirred at room temperature for 15 minutes. Acetone (25 mL per mmole of reagents) was then added, the precipitated sodium chloride was filtered off by passage through a Buchner funnel, and the acetone was removed by rotary evaporation. The resulting NIS was dissolved in 4:1 (v:v) CH_2Cl_2 : THF (25 mL per mmole of reagent), the trialkylsilyl ether (0.75 molar equivalents, relative to the NIS) was added, and the reaction mixture was stirred at room temperature under a dry nitrogen atmosphere for 1-2 hours. The resulting reddish yellow solution was partitioned between saturated sodium sulfite and dichloromethane, and the dichloromethane extracts were washed with saturated sodium bicarbonate solution, then dried over magnesium sulfate, filtered and concentrated in vacuo. After NMR analysis (to discern diastereomer ratios), the crude product was submitted to flash chromatographic purification (98:2 hexanes : ethyl acetate eluent) to yield the clean products in the yields indicated in Table 1.

13. The recipe followed was that of Jeffery, T. *Tetrahedron Lett.* **1985**, *26* , 2667-2670.

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