Pergamon

Tetrahedron Letters, Vol. 37, No. 22, pp. 3819-3822, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00722-8

DIASTEREOSELECTIVE ADDITION OF ALKYNYLSTANNANES TO ALPHA STANNYL SUBSTITUTED MIXED ACETALS: SYNTHESIS OF PRECURSORS FOR ALLENYL CARBINOLS

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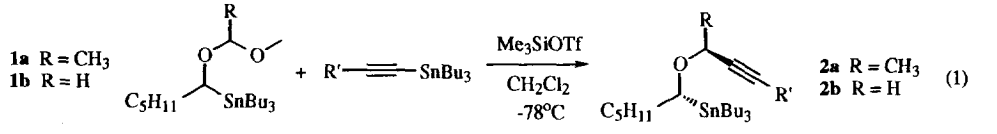
Abstract The regio- and stereoselective addition of alkynylstannanes to stannyl substituted mixed acetals results in propargylic ether derivatives in excellent yields.

Methods for the construction of five membered oxacyclic compounds are important for the synthesis of a number of classes of natural products. Marshall and co-workers have developed an efficient method for the synthesis of dihydrofurans by a silver (I) catalyzed cyclization of allenyl carbinols. [1] Furans are also readily formed in a similar fashion from the derived allenyl ketones. [2] Methods for the synthesis of the allenyl alcohol precursors have involved [2,3]-Wittig rearrangement of α-propargyloxy acetates and the Still-Wittig rearrangement of stannyl substituted propargylic ethers. [3] However, this novel approach to dihydrofurans is limited by the availability of the allene precursors. [1] This limitation is due to the fact that the Still-Wittig rearrangement is typically restricted to transmetallation of tributylstannylmethanol derivatives. [4] We recently published a stereoselective method for the synthesis of stannyl substituted alkyl / allyl ethers by the nucleophilic addition of vinyl copper species to stannyl substituted mixed acetals. [5] We now wish to report the extension of this chemistry to the direct addition of alkynylstannanes to stannyl substituted mixed acetals.

β-Stannylethynyl ethers and dialkyl amines have been shown to be effective nucleophiles for alkynylation of a number of reactive electrophilic species such as acid chlorides, isocyanates, ketenes, or carbodiimides. [6] We are aware of one example of the Lewis acid catalyzed alkynylation of a ketone; however, alkyl or aryl substituted alkynylstannanes were found to be generally unreactive. [7] The advent of palladium catalyzed coupling reactions has resulted in alkynylation of a number of substrates including aryl iodides, vinyl halides and vinyl triflates via the alkynylstannane. [8] However, there are apparently no reports of Lewis acid catalyzed reactions of acetals with alkynylstannanes.

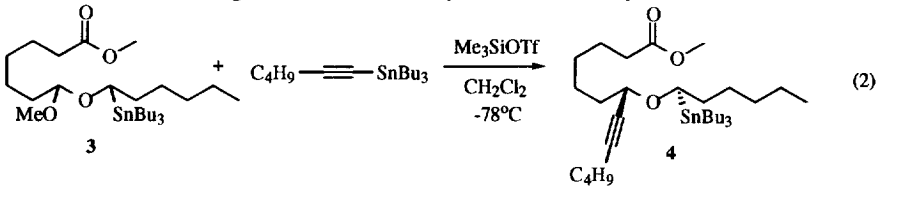
Non-commercially available alkynylstannanes were prepared from the corresponding lithium acetylide by the addition of chlorotributyltin. [9] The tributylstannyl derivative of ethyl propiolate was prepared from ethoxytributylstannane. [10] Initial reactions were carried out using alkynylstannanes and mixed acetal **1a** (1),



(1)

see the data in the Table. Our previous work on aldol and allylation reactions of stannyl substituted acetals led

us to use trimethylsilyltriflate as the Lewis acid for the reaction. [11] Given the initial success with TMSOTf, other Lewis acids have not been investigated. Optimum yields of the alkynyl addition products were obtained using 1.5 equivalents of the Lewis acid. Less than stoichiometric amounts resulted in somewhat lower yields. Ethynyltributylstannane, entry 1, did not provide the alkyne addition product **2a** (R'=H) in reasonable yield; however, the diastereoselectivity of the reaction was found to be >13:1 by GC analysis. It is interesting to point out that (1-tributylstannyl)(2-trimethylsilyl)ethyne reacted chemoselectively at the stannyl substituted carbon, providing the trimethylsilyl substituted alkyne product in 87% yield, entry 2. Phenyl and butyl substituted alkynes also resulted in the propargylic ether in excellent yields with selectivities greater than 13:1 (by GC), entries 3 and 4, respectively. Remote ether functional groups present on the alkyne moiety, benzyl and TBDMS ethers, were compatible under the reaction conditions and did not significantly effect the selectivity of the reaction, entries 5 and 6. However, a slightly reduced selectivity was observed for the benzyl ether case. The TBDMS ether was also susceptible to partial cleavage in reactions using more than 1.5 equivalents of TMSOTf. The dimethylamino and ester substituted alkynes, entries 7 and 8, were not effective coupling partners in this reaction and only led to decomposition products. In contrast, a remote ester functional group on the acetal can be tolerated (62% yield of **4** from acetal **3**, 7:1 diastereomeric mixture) as illustrated in (2). [12] It is interesting to note that the stannyl substituted formyl acetal derivative **1b** (1) is quite



(2)

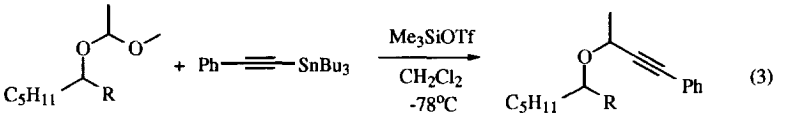
unreactive under the reaction conditions found to be optimum for alkyl substituted acetals such as **1a**. Indeed, less than 5% of the alkyne addition product **2b** (R'=Ph) was obtained in reactions of **1b** and (1-tributylstannyl)(2-phenyl)ethyne. Apparently an alkyl substituent must be present on the acetal carbon for efficient formation of an oxocarbenium ion intermediate.

Table Alkynylation Addition Product **2a**

	R'	Diastereoselectivity	Yield (%)
1	H	1 : 13.7	5
2	Me_3Si	1 : 11.4	87
3	Ph	>1 : 20	98
4	Bu	1 : 13.4	88
5	$BnO(CH_2)_3$	1 : 9.0	85
6	$TBDMSO(CH_2)_3$	1 : 14.0	92
7	Me_2NCH_2	-	-
8	EtO_2C	-	-

In all of the above cases, we have assigned the relative stereochemistry of the products as *anti* (as shown) based upon our earlier work. [5,11] The diastereoselectivity observed in the reactions of acetal **1a** is presumed to arise by selective addition to an oxocarbenium ion intermediate. The facial selectivity of the reaction is controlled not only by a steric effect, but by a stereoelectronic effect imparted by the tributyltin

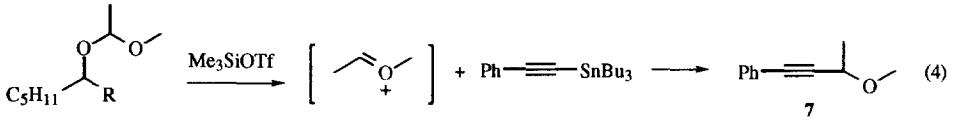
group. [11] Since acetal **1a** is prepared as a 1:1 mixture of diastereomers (GC), the alkyne addition reaction reported herein cannot occur via a direct S_N2 reaction. To test the importance of the stereoelectronic effect of the tributylstannyl substitutent on the reaction, the addition of alkynylstannanes to non-stannyl-substituted mixed acetals **5a** and **5b** was also examined. As anticipated, the alkyne addition reaction occurs in good yield, but in a non-stereoselective fashion. For example, the reaction of mixed acetal **5a** and (1-tributylstannyl)(2-phenyl)ethyne provided the adduct **6a** in 91% yield as a 1:1.1 diastereomeric mixture, while **5b** provided the adduct **6b** in 80% yield as a 1:1.2 diastereomeric mixture (3).



5a R = cycloHex
5b R = iPr

6a R = cycloHex
6b R = iPr

Furthermore, the addition reaction for acetal **5a** and **5b** is not completely regioselective. The regioisomeric product **7** was identified in both of the reactions with acetal **5a** and **5b**, in 5% and 12% yield, respectively. This regioisomer is derived from formation of the other possible oxocarbenium ion intermediate from the acetal (4). The analogous regioisomeric product was not observed in reactions of the stannyl

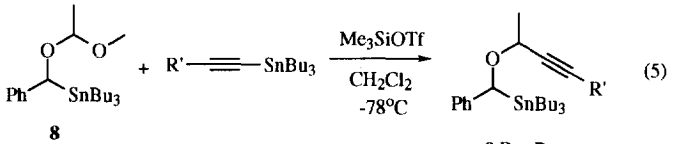


R = cycloHex or iPr

7

substituted acetal **1a** with any of the alkynylstannanes examined. [13] These data imply that a single oxocarbenium ion regioisomer is formed from the stannyl substituted mixed acetals by loss of the methoxy group. As in our previous work, these results show that the stannyl substituent is required for regio- and stereoselective addition of the alkynylstannane.

Surprisingly, reaction of stannyl acetal **8** with phenyl or butyl substituted alkynylstannanes provided the propargylic ethers **9** and **10** in very good yields, but the selectivity of the reaction was dramatically reduced (5). Indeed, both of the alkynyl addition products **9** and **10** derived from acetal **8** were obtained with less than 2:1 selectivity. We have no explanation for this contrasting behavior for the benzaldehyde derived acetal **8** and additional experiments are underway.



8

9 R = Bu
10 R = Ph

The addition of alkynylstannanes to stannyl substituted mixed acetals results in very good yields of stannyl substituted propargyl ethers which can be used as precursors for the synthesis of substituted allenyl carbinols via the Still-Wittig rearrangement. This stereoselective route is efficient, and provides a higher degree of substitution on the allene than possible by previously reported methods. [14]

Acknowledgments Financial support from the National Institutes of Health (GM47275) is gratefully acknowledged.

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12. The diastereoselectivity in this example, **4**, was determined by integration of the ^{1}H-NMR signals for the methine proton adjacent to the tributyltin substituent. The diastereoselectivity of the addition products **2a** given in the Table was determined by GC analysis of crude reaction mixtures. The diastereoselectivities of the addition products **9** and **10** were also determined by ^{1}H-NMR integration.

13. No methoxy signals corresponding to the methyl ether derivative were observed in the ^{1}H-NMR spectra of crude reaction products from acetals **1** or **8**. The regioisomeric ether **7** was easily identified in the ^{1}H-NMR by the methoxy signal at 3.48 ppm and the methine quartet at 4.29 ppm.

14. *Experimental* The stannyl substituted mixed acetal (0.1 mmol) and alkynylstannane (0.2 mmol) were dissolved in 6mL of CH_2Cl_2 and cooled to -78°C under an atmosphere of Ar. TMSOTf (0.15 mmol) was then added dropwise via syringe. The reaction mixture was stirred at -78°C for 2h and then quenched by the addition of 5mL of water. The reaction mixture was allowed to warm to room temperature, diluted with 100mL of ether, and the organic layer separated and dried over $MgSO_4$. The product was purified by flash chromatography (SiO_2) using hexane as the eluent. All new compounds exhibited correct spectral and analytical (CH combustion, MS) data.

(*Received in USA* 28 *March* 1996; *revised* 12 *April* 1996; *accepted* 16 *April* 1996)