Tetrahedron Letters, Vol.32, No.28, pp 3329-3332, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

STEREOSELECTIVE SYNTHESES OF DI-, TRI-, AND TETRASUBSTITUTED ENEDIYNES FROM ENYNYL IODIDES VIA Pd-CATALYZED COUPLING REACTIONS

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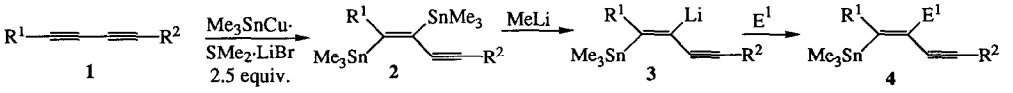
Abstract: Palladium catalyzed cross-coupling of iodoenynes derived from mono(stannyl)enynes with alkynyl zinc reagents affords isomerically pure conjugated di-, tri- and tetrasubstituted (Z)-enediynes and trisubstituted cross-conjugated enediynes in high yields.

Recently we have shown that the reaction of 1-(trimethylsilyl)-1,3-diynes **1**[1] with (trimethylstannyl)copper proceeds in a chemo- and regioselective manner to generate the corresponding *(E)*-bis(trimethylstannyl)enynes **2**. These bis(stannyl)enynes undergo stepwise transmetalation with methyllithium to furnish the corresponding enynyllithium reagents **3**. Elaboration of these via alkylation and protonation provide a variety of stereodefined mono(stannyl) enynes **4**.[2]

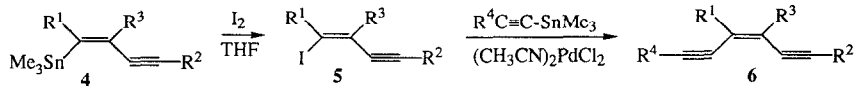


R^1 = alkyl; R^2 = $SiMe_3$; E^1 = R-X, or MeOH

An important aspect of our ongoing research on the synthetic utility of mono(stannyl)enynes as intermediates in organic synthesis is their elaboration into iodoenynes and, via further reaction of these, into stereodefined enediynes. It has been found that one group of exceptionally potent antitumor protein complexes contains as active agents calicheamicin γ_1 and esperamicin A_2.[3] These bicyclic compounds embody the enediyne moiety which has been intimately linked to their ability to cleave double-stranded DNA.[4] A number of elegant syntheses of the nonproteinal component containing the enediyne structural feature of antitumor agents have been reported.[5] Moreover, simpler variants of compounds containing the enediyne moiety have also been synthesized and used for mechanistic studies.[6] Recently, Nicolaou and coworkers prepared the first synthetic mimic of the calicheamicin-esperamicin class of antibiotics possessing DNA-cleaving properties.[7] The medicinal value of these compounds clearly points to the importance of methods for the design of enediyne analogues. Access to new chemotherapeutic agents might be provided by the prospect of developing diversely functionalized enediynes via the stannylenyne route.

Stille has shown that vinyl iodides undergo palladium-catalyzed cross-coupling reactions with a variety of acetylenic tin reagents, and that these reactions tolerate a wide variety of functional groups in either partner.[8] Hence, we explored the possibility of coupling iodoenynes with tin alkynylides in the presence of an appropriate palladium catalyst as a novel approach for the preparation of stereodefined enediynes. As a model, we investigated the coupling of iodoenyne **5** with 1-trimethylstannyl-1-hexyne in the presence of Pd(II) (eq 1). The iodoenyne **5** was readily available in quantitative yield by treatment of stannylenyne **4**[2] with a solution of iodine (1.1 equiv) in THF at

0°C. Reaction of **5** in the presence of 5-mol% of $Pd(CH_3CN)_2Cl_2$ with 1.3 equiv of the tin acetylide, derived from the lithium acetylide and trimethyltin chloride, afforded the (Z)-enediyne **6** in 74% isolated yield.

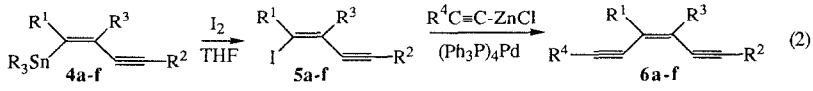


(1)

$R^1 = C_6H_{13}$; $R^2 = SiMe_3$; $R^3 = H$; $R^4 = C_4H_9$

To determine optimal conditions for the coupling reaction, the effects of the nature of the metal in the acetylenic reagent and the palladium catalyst upon the yield of the enediyne **6** formed were investigated. The results revealed that the zinc acetylide is superior to the tin acetylide. On the other hand, both $(Ph_3P)_4Pd$ and $(CH_3CN)_2PdCl_2$ gave comparable yields. However, the coupling reaction was completed faster, 2h vs 4h, when tetrakis(triphenylphosphine) palladium was used as the catalyst.

Having established optimal conditions for the preparation of the enediyne **6**, we investigated the introduction of different substituents onto the enediyne by varying the substitution pattern of the iodoenyne and the zinc acetylide. The results obtained in the Table clearly show that stannylenynes (**4**) are valuable precursors for preparation of the isomerically pure *(Z)*-iodoenynes **5a-f** and of the alkyl, phenyl and silyl-substituted enediynes **6a-f** (eq 2).



(2)

R3Sn: Me3Sn or $(n\text{-}C_4H_9)_3Sn$

Table. Yields of Iodoenynes **5** and Enediynes **6**

	R^1	R^2	R^3	R^4	Isolated yields,% [a]	
					5	**6**
a	C_6H_{13}	$SiMe_3$	H	*n*-C_4H_9	100	85
b	C_6H_{13}	$SiMe_3$	H	C_6H_5	100	87
c	C_6H_{13}	$SiMe_2$Thexyl	H	$SiMe_3$	93	79
d	C_6H_{13}	$SiMe_3$	CH_3	*n*-C_4H_9	99	80
e	CH_3	$SiMe_2$Thexyl	H	*n*-C_4H_9	87	86
f	H	$SiMe_2$Thexyl	H	*n*-C_4H_9	85	85

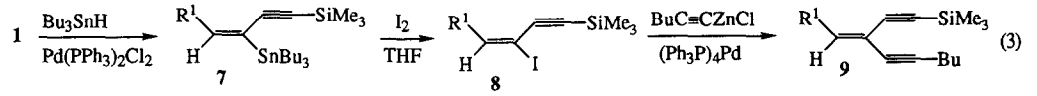
[a] The IR, ^1H NMR, ^{13}C NMR, and mass spectral data of the compounds are consistent with the assigned structures. NOE experiments were used to assign stereochemistry.

The following procedures for preparation of the iodoenynes **5a-d** and the enediynes **6a-d** are representative. To a solution of **4a-d**[2] (3.0 mmol) in THF (4 mL) was added at 0°C a solution of iodine (3.3 mmol) in THF (5 mL) over a 30 min period. The reaction mixture was stirred at room temperature for 90 min, then was treated with a saturated solution of sodium bisulfite. Extraction with pentane, washing the pentane extract with brine, concentration and passing the concentrate through a short silica gel pad using *n*-hexane furnished the

iodoenynes **5a-d**. To a mixture of **5a-d** (2.0 mmol), $Pd(PPh_3)_4$ (0.10 mmol) and THF (4 mL) maintained at 25°C was added dropwise via a double ended needle a cooled solution (ice bath) of the chlorozinc alkynylide (2.2 mmol), prepared from the corresponding lithium acetylide and anhydrous zinc chloride.[9] The resultant dark gold colored solution was stirred for 2 h, then was quenched by pouring into a separatory funnel containing 10 mL of H_2O. The layers were separated, and the aqueous phase was extracted with ether, the combined etheral layers were washed with brine, then dried ($MgSO_4$). Evaporation of the solvent and chromatography of the residue obtained on silica gel (60-200 mesh) using *n*-hexane afforded the enediynes **6a-d**.

In the case where R^1 is *n*-butyl or larger, the bis-stannation of diynes **1** is chemo- and stereoselective.[2] However, if R^1 is methyl or hydrogen, the bis-stannation is not stereoselective. Fortunately, utilization of the more hindered tributylstannyl lithium[10] instead of trimethylstannyl lithium for the preparation of the stannyl-copper reagent obviated the problem. Transmetalation of the resultant bis(tributylstannyl)enynes with methyllithium afforded, after protonation or alkylation the mono(tributylstannyl)enynes. However, purification of the compounds either by distillation or by chromatography on silica gel resulted in their partial isomerization. Therefore, the crude mono(stannyl)enynes were treated directly with 2.1 equiv. of iodine in THF to accomplish iododemetalation as well as cleavage of the methyltributyltin generating the desired iodoenynes **5e,f** and tributyltin iodide. Workup and chromatography of the concentrated reaction mixtures on silica gel with a 10:90 mixture of Et_3N/hexane afforded the pure iodoenynes, which were then elaborated stereospecifically into the enediynes **6e,f**.

We next investigated the preparation of cross-conjugated enediynes **9** via the palladium catalyzed cross-coupling reaction of iodoenyne **8** with chlorozinc hexynylide. Recently, it has been shown that cis-monohydrostannation of 1-trialkylsilyl-1,3-diynes **1** with *n*-Bu_3SnH in the presence of $(Ph_3P)_2PdCl_2$ produces the (monostannyl)enynes **7**.[11] Iododemetalation of the monostannyl enyne **7** with a solution of iodine (1.1 equiv) occurred cleanly and stereoselectively. Since the iodo enyne **8** formed tends to isomerize, the reaction mixture was treated with 5-mol% of BHT in THF prior to removal of THF solvent under vacuum. Addition of Et_3N (6 equiv) to the concentrate resulted in the precipitation of the tributyltin iodide by-product. The solid was triturated with *n*-hexane, and the mixture was filtered through a short silica gel pad. The iodoenyne **8** thus obtained was coupled with the acetylenic zinc in the presence of $(Ph_3P)_4Pd$ to furnish the cross-coupled enediyne **9** in 73% isolated yield based on **7** (eq 3).



$R^1 = n\text{-}C_6H_{11}$ (3)

In summary, the cross-coupling reaction of iodo enynes **5** and **8** with various zinc alkynylides provides a novel and valuable approach for the stereoselective syntheses of conjugated and cross-conjugated enediynes, respectively. These may be further elaborated by desilylation or desilylation-alkylation at the trialkylsilyl moiety into various substituted enediynes. Chemoselective desilylation of the trimethylsilyl group in the presence of the dimethylthexylsilyl group has been achieved by treatment of the enediyne **6c** with one equiv. of $KF{\cdot}2H_2O$ in DMF. In addition, the (trialkylsilyl)ethynyl moiety itself should be amenable to various transformations. Finally, the substituent at R^3 in **6** can be controlled by the appropriate choice of electrophile E^1 in **4**.

Acknowledgement: We thank the National Science Foundation (Grant CHE-8920731) for support of this research.

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10. The Me_3SnLi and *n*-Bu_3SnLi used for the preparation of the stannylcopper reagents were obtained by adding at room temperature trimethyltin chloride or freshly distilled *n*-tributyltin chloride (50 mmol), respectively, to a vigorously stirred mixture of dry THF (84 mL) and flattened lithium wire (110 mmol) containing 5% Na. After a short induction period, the reaction exothermed to 60°C. The flask was immersed into a 80W ultrasonic water bath (25°C), the mixture was sonicated for 2h, allowed to settle overnight, and the clear supernatant liquid was standardized by titration and then used for the preparation of the trialkyltincopper reagent.
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(Received in USA 2 April 1991)