ORGANIC LETTERS

1999
Vol. 1, No. 5
701−703

(*E*)-5-(Tributylstannylmethylidene)-5*H*-furan-2-ones: Versatile Synthons for the Stereospecific Elaboration of γ-Alkylidenebutenolide Skeletons

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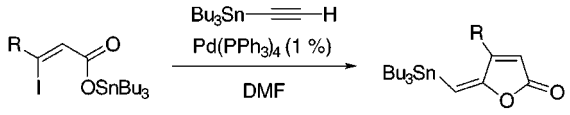
Received May 6, 1999

ABSTRACT



Stereoselective construction of (*E*)-γ-tributylstannylmethylidene butenolides 1 was achieved through the palladium-catalyzed tandem cross-coupling/cyclization reactions of tributylstannyl 3-iodopropenoate derivatives with tributyltinacetylene. Iododestannylation of 1 occurs with inversion of the configuration of the exocyclic double bond while the observed selectivity in the Stille reaction was found to be dependent on the nature of the aryl halide.

Due to their large abundance and their biological interest and potential medicinal value, butenolides have been extensively studied.[1] Over the past decade, an increasing amount of attention has been focused on the synthesis of stereodefined γ-alkylidene butenolides[2] which have been isolated from natural sources. For example, freelingyne[3] displays antibiotic activity and rubrolides,[4] which are marine tunicate metabolites, exhibit potent antibiotic activities in vitro. Principally, the γ-alkylidene butenolide moiety has been obtained by four major methods. Lewis acid catalyzed coupling of aldehydes or ketones with oxyfurans,[5] alkenylation of γ-lactones via their enolates[6] or phosphorus ylides,[7] and olefination of maleic anhydrides with organometallic reagents[8] or phosphoranes[9] were described as efficient methods but with a major drawback in the nonselective

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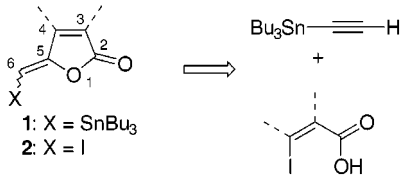
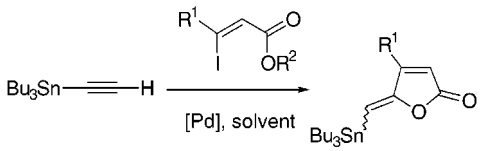
10.1021/ol9900764 CCC: $18.00
Published on Web 07/28/1999

Scheme 1



construction of the exocyclic double bond. The fourth one, a transition metal (Pd, Ag) catalyzed lactonization allows complete control of exocyclic alkene geometry.[10,11] In addition, we have previously described the synthesis of dienic acids or enynes bearing a carboxylic acid function from β-iodovinylic acid and vinyltin or alkynylzinc reagents.[12] This methodology was then applied to the synthesis of retinoic acids and certain analogues.[13] To broaden our synthetic strategy, we planned to prepare γ-alkylidenebutenolides **1** and **2** which we though would allow more flexibility in the construction of the above natural products and could theoretically be obtained from β-iodo vinylic acids and tributylstannylacetylene (Scheme 1).

Scheme 2



1a-e

Herein, we report a stereoselective synthesis of (*E*)-γ-(tributylstannylmethylidene)butenolides under palladium complex catalysis and the preliminary results about their reactivity.

Our investigation began with the coupling of tributylstannylacetylene with (*Z*)-3-iodoprop-2-enoic acid under conditions defined by Lu[14] or Negishi.[4b] Unfortunately, only a few traces of stannylated methylidenebutenolide **1a** were obtained in mixture with a large amount of tin byproducts and the starting iodovinylic acid.

To obtain good yields of **1**, we examined the reaction under various conditions (solvent, catalyst, presence of additives, . . .). The results are summarized in Table 1. In the first step, the influence of the nature of the carboxylic acid function on conversion rates was examined.

Table 1. Experimental Conditions for the Synthesis of **1a**[a]

entry[b]	R^2	[Pd]	add.	solvent	yield, %
1	H	A	CuI (10%) Et_3N	DMF	5
2	Et	A		DMF	*c*
3	Na	A		DMF	0
4	$SnBu_3$	A		DMF	67
5	$SnBu_3$	A		MeCN	0
6	$SnBu_3$	A		THF	0
7	$SnBu_3$	B		DMF	13
8	$SnBu_3$	C		DMF	54
9	$SnBu_3$	C	PPh_3	DMF	57
10	$SnBu_3$	A	CuI	DMF	60

[a] A = $Pd(PPh_3)_4$; B= $PdCl_2(MeCN)_2$; C= $PdCl_2(PPh_3)_2$. [b] These attempts were performed with (*Z*)-3-iodoprop-2-enoic acid (R^1 = H). [c] Ethyl pent-2-en-4-ynoate was obtained in 73% yield.

In DMF and in the presence of 1% tetrakis(triphenylphosphine)palladium, free carboxylic acid (entry 1), ester (entry 2), and sodium salt derivatives (entry 3) did not yield the desired tin butenolides **1**. Surprisingly, the use of tributyltin carboxylate (entry 4), under identical conditions to those above, gave in 67% yield **1a** with a clean configuration of the double bond. Next were examined the nature of the solvent and of the palladium complexes. Acetonitrile and THF (entries 5 and 6) were found to be ineffective while DMF (or dimethylacetamide) afforded cyclized product in fair yields. We equally observed that phosphine ligated palladium appeared to be more efficient than other palladium salts such as palladium acetate or bis(acetonitrile)palladium chloride (entry 7). Attempts to further improve the yield by using copper salt met with no success (entry 10).

1a was easily purified by column chromatography, and its structure was attributed by ^{1}H and ^{13}C NMR. According to the above authors, a (*Z*)-isomer of **1a** was expected. Analysis of tin−carbon coupling constants, which was previously reported to be a good tool to attribute the stereochemistry of trisubstituted vinystannanes,[15] revealed a very low $^3J_{Sn-C4}$ (17 Hz) coupling constant, indicating a preference for the (*E*)-isomer. A NOESY experiment conducted on **1a** gave a strong cross-peak between H_4 and α-CH_2 of Bu_3Sn group and no cross-peak between H_4 and H_6 and confirmed the *E* configuration.

Reaction of tributylstannyl acetylene with a range of tributylstannyl (*Z*)-3-substituted 3-iodoprop-2-enoates pro-

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(12) (a) Duchêne, A.; Abarbri, M.; Parrain, J.-L.; Kitamura, M.; Noyori, R. *Synlett* **1994**, 524. (b) Abarbri, M.; Parrain, J.-L.; Duchêne A. *Tetrahedron Lett.* **1995**, *36*, 2469. (c) Abarbri, M.; Parrain, J.-L.; Cintrat, J.−C.; Duchêne A. *Synthesis* **1996**, 82. (d) Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchêne, A. *Main Group Metal Chem.* **1997**, *20*, 195.

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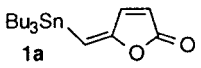
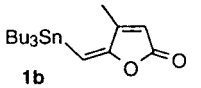
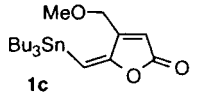
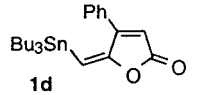
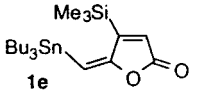
ceeded with regio- and stereocontrol to give (*E*)-5-tributylstannylmethylidene-5*H*-furan-2-ones **1a**−**e** in fair yields (Table 2).

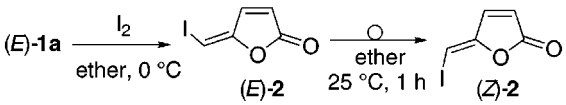
Table 2. Synthesis of (*E*)-5-(Tributylstannylmethylidene)-3-substituted-5*H*-furan-2-ones

entry	R^1	**1**	Yield (%)
1	H	 **1a**	67
2	Me	 **1b**	62
3	Me-O-CH_2	 **1c**	70
4	Ph	 **1d**	67
5	Me_3Si	 **1e**	65

No isomerization of the double bond was observed and no cyclization, affording pyranones, occurred as previously observed under Sonogashira conditions.[3b,16] Moreover, Stille cross-coupling products derived from **1a** and the starting iodopropenoic acid were not detected. It is clear from these preliminary experiments, although somewhat difficult to rationalize, that all the desired compounds **1a**−**e** were obtained with full preference for the (*E*)-isomer (the stereochemistry was assigned on each case via the $^{13}C-^{119}Sn$ coupling constants).

Attention was next directed to the reactivity of tin butenolides **1a**−**e**. The iododestannylation of **1a** occurred stereospecifically in ether at 0 °C in good yield. (Scheme 3).

Scheme 3

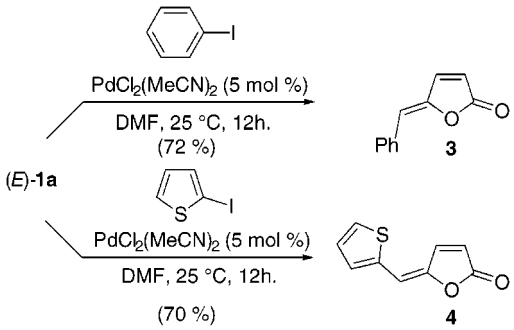


Nevertheless, the iodobutenolide (*E*)-**2** was found to be unstable and quantitatively isomerized into the (*Z*)-isomer. Attempts to stabilize (*E*)-**2** by lowering the temperature or changing the solvent (toluene, chloroform, or dichloromethane) were unsuccessful and yielded mixtures of isomers which, after few hours, led to the thermodynamically more stable (*Z*)-isomer.

(16) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713 and references therein.

Finally, Stille cross-coupling[17] of **1a** with iodobenzene in the presence of a catalytic amount of dichlorobis(acetonitrile)palladium(II) (5%) in DMF gave the desired arylbutenolide in 72% yield (Scheme 4) but with an inversion of the configuration of the exocyclic double bond with respect to the stereochemistry of the starting tin product.

Scheme 4



This can be explained by the greater thermodynamic stability of the (*Z*)-isomer of **3**. The AM1 semiempirical calculation method applied to both isomers of **3** reveals for the isomer (*E*)-**3** (certainly formed during the cross-coupling) a substantial interaction of the hydrogen borne by the C4 carbon of the furanone cycle and the hydrogens in the ortho position of the benzenic ring.[18] In contrast, an identical attempt performed with 2-iodothiophene led to the desired thienyl methylidene butenolide **4** with a clean *E* configuration of the exocyclic double bond, again demonstrating that Stille coupling occurs with retention of configuration.

In conclusion, we have demonstrated that the palladium-catalyzed tandem cross-coupling/cyclization reactions of tributylstannyl 3-iodopropenoate with tributyltinacetylene affords with fixed configuration of the double bond (*E*)-γ-tributylstannylmethylidene butenolides which are the potential precursors of numerous alkylidenes butenolides. Current studies are aimed at increasing our mechanistic understanding of butenolide formation as well as broadening the application of such reagents toward the synthesis of natural alkylidene butenolides.

Acknowledgment. We thank the CNRS and MENRT for providing financial support and the Service d'analyse chimique du vivant de Tours for recording NMR and mass spectra.

Supporting Information Available: Typical experimental procedure for the preparation of **1a**−**e**, **2**, and **3**−**4.** Tabulated ^1H, ^{13}C,and ^{119}Sn NMR and mass data for **1a**−**e**, **2**, **3**, and **4**. ^1H, ^{13}C, and ^{119}Sn NMR spectra for **1a**−**e** and NOESY or NOE difference spectra of **1a**, **3**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) AM1 calculations were performed by the Hyperchem package on a PC computer. (*Z*)-**3**: $E = -2418.816$ kcal·mol^{-1}. (*E*)-**3**: $E = -2416.067$ kcal·mol^{-1} (rms energy gradient <0.001).