

E- and Z- β -Formylvinyl Synthons from 1-Tributylstannyl-3,3-diethoxy-prop-1-ene via Cross Coupling with Acid Chlorides

**Jean-Luc Parrain^a, Isabelle Beaudet^a, Alain Duchêne^b,
Sandrine Watrelot^a and Jean-Paul Quintard^{a*}**

a) Laboratoire de Synthèse Organique associé au CNRS, Faculté des Sciences
et des Techniques de Nantes, 2 rue de la Houssinière - 44072 Nantes - Cedex 03. (France).

b) Laboratoire de Synthèse et d'Etudes Physicochimiques Organiques,
Faculté des Sciences de TOURS, Parc de Grandmont - 37200 Tours. (France).

Abstract : The easily prepared and stored E-1-tributylstannyl-3,3-diethoxy-prop-1-ene 1E reacts with acyl chlorides in DMF in the presence of PdCl₂(MeCN)₂ to give the expected 1,4-ketoacetals (E isomers). Similarly cross coupling of 1E with tosyl chloride performed in THF in the presence of Pd(PPh₃)₄ affords the E- β -diethoxymethylvinylsulphone whose metallation with MeLi, LiBr generates a β -formylvinylanion equivalent with the anionic centre in a cis relationship relative to the diethoxymethyl group.

Due to their umpolung character, the β -formylvinylanion equivalents are of great interest in organic chemistry¹, providing a challenge for the elaboration of more suitable precursors than those which are currently available. Initial proposals involved mainly allylic metallation of 1,3-bis(organothio)prop-1-ene², 1,3-bis(arylseleno)prop-1-ene³, 1-methoxy-3-phenylthioprop-1-ene⁴ or S-allyldithiocarbamates⁵ but despite improvements brought about by the use of thiophilic cations^{2,6}, the deprotection step (for instance conversion of dithioderivatives into α,β -enals) often appears to be a limiting step in terms of yields. β -sulphonylated propionaldehyde acetal⁷, phosphorus⁸ or arsenic ylides⁹ as well as (α -alkoxyallenyl) silanes¹⁰ have also been used for such a purpose, but in every case a lack of quality is observed, the limiting factors appearing to be in terms of yields, generality of the method or accessibility to the precursor.

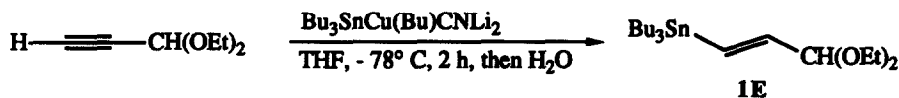
Another interesting approach has been proposed by Meyers starting from E- β -bromoacrolein diethylacetal¹¹. Reaction with tert-butyllithium leads principally to halogen-metal exchange, while reaction with n-butyllithium gives mainly the α -bromovinyl lithium reagent after vinylic hydrogen abstraction ; however, in each case the competition between metallation and halogen-metal exchange gives a mixture of the two anionic species and requires use of very low temperature (-120°C) in the case of E-1-lithio-3,3-diethoxyprop-1-ene in order to avoid its decomposition.

Recently we have shown that 1-tributylstannyl-3,3-diethoxyprop-1-ene can be a valuable β -formylvinylanion equivalent¹². Transmetallation of this reagent with n-butyllithium at -120°C affords the expected *trans* vinyl lithium, but, more interestingly, its transmetallation with n-Bu₂CuCNLi₂ in THF leads to the

corresponding vinyl cyanocuprate at room temperature. Furthermore 1-tributylstannyl-3,3-diethoxyprop-1-ene gives cross coupling products with aryl and heteroaryl halides under palladium complexes catalysis¹².

In spite of these promising results, this initial work has to be improved on two points:

- The vinyltin reagent must be obtained as a single isomer, instead of the usual thermodynamic mixture of the vinyltin isomers afforded by free radical hydrostannation of 3,3-diethoxyprop-1-yne. We have already solved this problem¹³ *via* tributylstannylcupration of 3,3-diethoxyprop-1-yne with Lipshutz reagent¹⁴.



- Another difficulty arose when cross coupling of 1E with acyl halides was attempted because of a competitive reaction with the acetal function.

We wish herein to report an efficient procedure to circumvent this difficulty and to transfer efficiently the β -formylvinyl unit with a clean control of configuration (complete control of the E or Z relationship between the anionic centre and the diethoxymethyl group being obtainable from 1E).

When the cross-coupling of 1E with acyl chlorides was attempted in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ using benzene as solvent, the Lewis acidity of the acyl chloride induced a reaction at the labile allylic acetal function instead of a reaction at the tin-carbon bond. This result means that we have to use a solvent which is basic enough to moderate the electrophilic character of the acid chloride. A first attempt using benzoyl chloride in the presence of triethylamine (1eq.) allowed this type of coupling but this method was ineffective with aliphatic acyl chlorides owing to the formation of acyl ammonium salts and subsequent β -elimination. This methodology had to be improved using a more appropriate solvent and on the basis of previous reports¹⁵ and personal observations¹⁶ our final choice was the use of DMF as solvent and $\text{PdCl}_2(\text{MeCN})_2$ as catalyst.

By this route, the reaction of 1E with acid chlorides becomes general, the monoprotected 1,4-ketoaldehydes being obtained in high yields (cf table I).

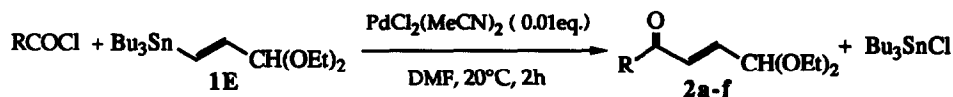
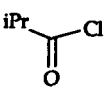
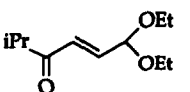
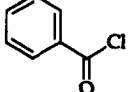
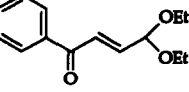
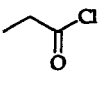
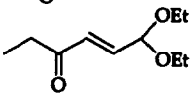
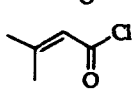
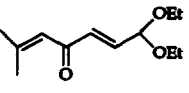
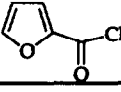
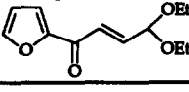
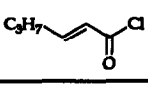
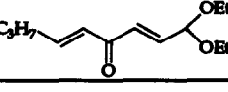
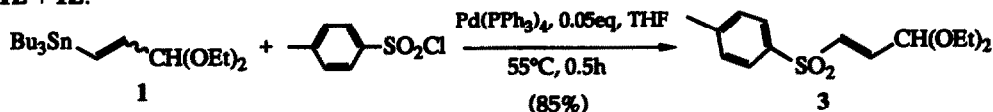


Table I: Cross coupling of 1E with acid chlorides

RCOCl	1,4-Ketoacetal	N°	%	RCOCl	1,4-Ketoacetal	N°	%
		2a	83			2d	75
		2b	89			2e	57
		2c	78			2f	85

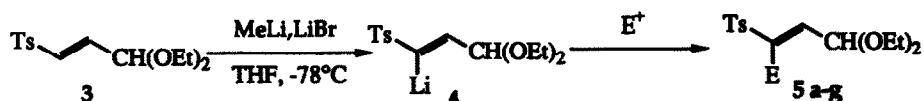
Whatever the nature of the R group (alkyl, vinyl, aryl or heteroaryl), the reaction remains possible and it is worth noticing that the presence of branched alkyl groups on the substrate is well tolerated.

An extension of this reaction to cross coupling of **1** with tosylchloride has been attempted under the experimental conditions used previously with other vinyltins¹⁷. The expected coupling was observed and due to its higher stability, the vinylic sulphone **3** was obtained in the E configuration only, starting from a mixture of **1E** + **1Z**.



Compared with other syntheses of **3**¹⁸, this cross coupling constitutes an attractive preparation for a useful compound in organic synthesis¹⁹. Focussing on anionic chemistry and considering the results reported for

β -acyl-vinylanion equivalents²⁰, **3** appears to be a potential precursor of a β -formylvinyl-anion equivalent having a *cis* relationship between the anionic centre and the acetal group. Indeed, the reaction of **3** with the complex MeLi₂LiBr in THF for 1h at -78°C affords the α -lithiated vinylic sulphone **4** according to:



Electrophilic trapping of **4** with D₂O, aldehydes and miscellaneous halides affords the expected 2-substituted vinylic sulphones (**5 a-g**) in moderate to good yields (cf table II).

Table II: Reaction of **4** with electrophiles

E ⁺	5	N ^o	Yield	E ⁺	5	N ^o	Yield
D ₂ O		5a	44%	Me ₂ C=CHCHO		5e	56%
MeI		5b	50%	Et ₂ CH-CHO		5f	71%
Me ₃ SiCl		5c	90%			5g	68%
PhCOCl		5d	35%				

With some substrates, it is worth noticing that side reactions may occur to an important extent. For instance, the reaction of **4** with benzaldehyde appears to be complicated by the formation of benzylic alcohol (reduction product, possibly due to the occurrence of a mono-electronic transfer mechanism), while reaction of **4** with acetophenone affords the Michael adduct of acetophenone enolate on sulphone **3** as already reported in the case of anionic species generated from functional sulphones²¹.

In spite of these complications, the possible reduction²² of sulphones **5** means that vinyltin **1E** can be considered as a β -formylvinyl anion equivalent allowing alternatively E or Z stereochemical control of the β -formylvinyl unit.

Typical procedure: A DMF solution of acid chloride (10 mmol in 15 ml of dry DMF) was placed in a Schlenk tube and degassed before addition of **1E** (4.2 g, 10 mmol) and PdCl₂(MeCN)₂ (25 mg, 0.1 mmol). The pale yellow mixture turned progressively brown-red after 2 hours at room temperature. At this time, 20 ml of an aqueous solution of sodium fluoride and 20 ml of acetone were added in order to remove tributyltin chloride. After the extraction and usual treatments, compounds **2a-f** were purified on silica gel (hexane / ether / triethylamine: 92/6/2). For compounds **3** and **4**, the previously described methods^{17, 20} have been used with success (with a temperature of -78°C for the generation and the trapping of **4**).

Acknowledgements : *The authors are grateful to Chemetall GMBH, Schering and Rhône-Poulenc Societies for the gift of organometallic starting materials.*

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(Received in France 7 June 1993; accepted 2 July 1993)