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Stannylation of Acetylenic Acids: a Stereoselective Access to Functionalized α,β - and β,γ -Unsaturated Acids

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Abstract: *The stereoselective synthesis of vinylstannanes bearing carboxylic acid function was achieved from acetylenic acids via stannylcupration reaction. In homoallylic series, regioselectivities are highly dependant on the nature of stannyl anionids and on the protection of the carboxylic acid function.*

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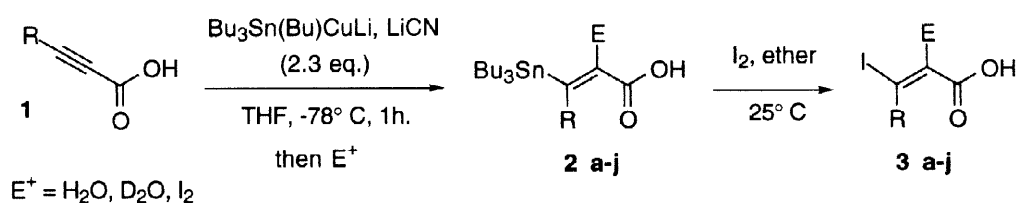
keywords: acetylenic acids, stannylation, vinylstannanes, vinyl iodides, α,β - and β,γ -unsaturated acids.

Over the last decade, functionalized vinyltin reagents have emerged as valuable tools for organic synthesis.¹ Due to the wide possibilities especially palladium catalysed cross-coupling to transfer a vinyl unit, they are used in a key step in total synthesis.² The synthesis of vinyltin reagents was historically obtained through radical hydrostannation of alkynes.³ However, this method was found to be limited because of its low selectivity, and numerous methods such as transition metal catalysed hydrostannation^{3,4} have been proposed to resolve this problem. Among these, the stannylcupration reaction of alkynes generally offers good regio- and stereoselectivities.⁵⁻⁹ Moreover, the intermediate vinyl copper can be alkylated affording trisubstituted vinylstannanes.^{5-6,8,10,11} Interestingly, the stannylcopper reagents were found to be inert at low temperature towards hydroxy or NH amide functions.^{7,12-16}

As a part of a program dealing with the reactivity of unprotected iodovinyl acids and organometallic reagents under palladium complexes catalysis,¹⁷ we planned to study the obtention of numerous vinylstannanes or vinyl iodides bearing an unprotected carboxylic acid function. In a precedent report related to the use of tributylstannyl 4-tributylstannylbut-3-enoate as a C-4 homologating agent, we described that the radical hydrostannation of homopropargylic acids afforded vinylstannane with poor *E/Z* selectivities.¹⁸

In this paper we now report the selective obtention of functional allylic and homoallylic acids by stannylation of alkynoic acids. Stannylation reaction of alk-2-ynyl esters or amides has been extensively studied by Piers who demonstrated that the obtained stereoselectivities are dependant on the nature of the stannylcuprate reagents, the temperature and the solvent.¹⁹ To the best of our knowledge, no attention has been paid to stannylation reaction of acetylenic acids. Initially, our attention was directed towards stannylation of but-2-ynoic acid since the radical hydrostannation of propiolic acid was described to give poor *E/Z* selectivity.²⁰ Numerous tin anionid systems known to add to triple bond were tested. When using $\text{Bu}_3\text{SnAlEt}_2/\text{CuCN}$ **A**,²¹ $\text{Bu}_3\text{SnMgMe}/\text{CuCN}$ **B**,⁶ $(\text{Bu}_3\text{Sn})_2\text{Zn}/\text{Pd}(\text{PPh}_3)_4$ **C**,⁶ only low conversion rates into (*E*)-3-tributylstannylbut-2-enoic acid were obtained. The best results were obtained with high order

$\text{Bu}_3\text{Sn}(\text{Bu})\text{CuLi}$, LiCN cyanocuprate **D** (2.3 eq.)¹⁶ affording the same isomer with fair yields. As already evocated¹⁵ a clean cis-addition of stannylcuprate occurred and no Bu ligand was transferred to the triple bond.



To extend this study, various 3-substituted alk-2-ynoic acids were transformed into vinylstannanes²³ and, after subsequent iodine treatment, into the more stable vinyl iodides. Results are recorded in table 1. In each case, complete regio- and stereoselectivity occur.

Table 1 : Stannylcupration of 3-substituted alk-2-enoic acid

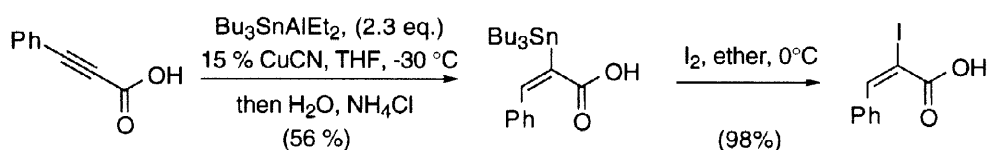
Entry	R	E	2	Yield (%) ^a	3	Yield (%) ^b
1	H	H	2a	65	3a	58
2	Me	"	2b	63	3b	56
3	Et	"	2c	68	3c	60
4	<i>n</i> -Pr	"	2d	64	3d	57
5	<i>n</i> -Pent	"	2e	72	3e	66
6	Ph	"	2f	62	3f	59
7	Me_3Si	"	2g	55	3g	51
8	MeO-CH_2	"	2h	72	3h	63
9	Me	D	2i	60	3i	58
10	Me	I	2j	45	3j	38

a : Conversion rate based on **1**

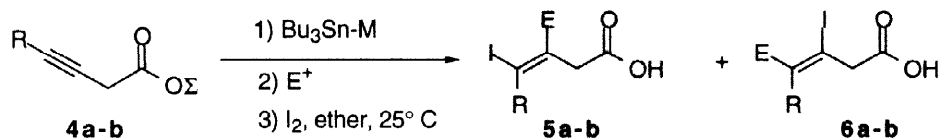
b : Reported yields correspond to isolated products based on alkyenoic acids **1**

Attempts to incorporate a methyl group by quenching the vinylcopper intermediate with methyl iodide failed even in the presence of 30 eq. of HMPA⁷ (this result is in agreement with those observed in the stannylcupration of diethoxypropyne⁹). It should be noted that for iodine quenching (entry 10), a complete reaction was only observed after 48 h at 0°C . On the basis of a recent report relative to the stannylcupration in the presence of methanol, we observed that adding MeOH (5 eq.) contributes to a slight increase of the yields (4-7%).²²

In the case of 3-phenylprop-2-ynoic acid, a reverse regioselectivity could be obtained when using tributylstannyl diethyl aluminium in presence of a catalytic amount of copper cyanide (10%) as described in the following scheme.



To broaden the scope of the preparation of vinylstannanes or vinyliodides bearing carboxylic acid function, we investigated the stannylmetallation reaction of homopropargylic acids as described in the scheme below. Results are recorded in table 2.



Identically to stannylcupration of propargylic acids, best results (yield and regioselectivity) were obtained with the high order cyanocuprate **D** (entry 1) which provided, after iodine treatment, a 95/5 mixture of terminal and internal regioisomers (entry 1-2). Other tin anionid reagents gave poor regioselectivities but with a reverse trend (entry 3-5).

Table 2 : Stannylmetallation of alk-3-ynoic acids

entry	R	Σ	E	M	Tin reagent	5 ^e /6	yield (%)
1	H	H	H	Cu(Bu)Li, LiCN ^a	D	95/5	55
2	H	H	D	Cu(Bu)Li, LiCN ^a	D	95/5	53
3	"	"	H	AlEt ₂ , 15% CuCN ^b	A	20/80	28
4	"	"	"	MgMe, 15% CuCN ^c	B	70/30	35
5	"	"	"	ZnSnBu ₃ , [Pd] ^d 5%	C	67/33	40
6	H	SnBu ₃	"	Cu(Bu)Li, LiCN ^a	D	5/95	47
7	"	SnBu ₃	"	MgMe, 15% CuCN ^c	B	30/70	53
8	Et	H	"	Cu(Bu)Li, LiCN ^a	D	90/10	40
9	H	H	Me	Cu(Bu)Li, LiCN ^a	D	98/2	55

a: THF, -78°C, 1h; b: THF, -30°C, 3h; c: THF, 0°C, 2h; d : [Pd]= Pd(PPh₃)₄; e: only the *E* isomer is obtained

In order to acquire information regarding to the influence of the carboxylic acid function protection, tributylstannyl ester of but-3-ynoic acid (entry 6) was found to react with **D** with a completely reverse regioselectivity in comparison with entry 1. Similarly, stannylanionid **B** gave a 70/30 mixture in favour of the terminal vinylstannane (entry 7). The stannylcupration of hex-3-ynoic acid (entry 8) with **D** confirmed the regioselectivity of the addition. Finally, treatment of vinylcopper intermediate (entry 9) with methyl iodide led to trisubstituted vinylstannanes in fair yield but with excellent regioselectivity. Concerning the factors governing the regioselectivity of the addition reaction it seems difficult to predict the trend of the addition which can be reversed by a slight change in the nature of both alkynes and stannyl reagents.

In summary the stannylcupration reaction of alkynes provided numerous functional vinylstannanes and vinyliodides. Studies are now under way to delineate the synthetic utility of these reagents and the results of these investigations will be reported in due course.

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23. General procedure for obtention of vinyltin **2**. Tributyltin cuprate is prepared according to the general route outlined by Lipshutz.¹⁵ CuCN (1.8 g, 20.17 mmol) is suspended in freshly distilled THF (60 mL), cooled at -78°C and treated with 1.6 M BuLi in hexane (25.2 mL, 40.35 mmol). The mixture is allowed to react for 15 min and then Bu₃SnH (10.85 mL, 40.35 mmol) is added dropwise. After stirring for 10 min at -78°C, 4-methoxybut-2-ynoic acid (1g, 8.77 mmol) diluted in THF (10 mL) is added and allowed to react for 1h. The reaction mixture is quenched with saturated NH₄Cl solution at -78°C and diluted with Et₂O. The organic layer is separated, washed with brine (30 mL) and dried over MgSO₄. After evaporation of solvents, the crude product **2h** is purified by column chromatography on silica gel (petroleum ether/Et₂O, 50/50, then CH₂Cl₂). IR (cm⁻¹) : 1685, 1660; ¹H NMR δ (ppm) (200 MHz): 0.9 (15H, m), 1.26-1.70 (12H, m), 3.33 (3H, s), 4.55 (2H, d, ⁴J_{1H} = 1.2Hz, ³J_{Sn-H} = 28Hz), 5.95 (1H, t, ⁴J_{2H} = 1.2Hz, ³J_{Sn-H} = 65Hz), 11.1 (1H, bs) ¹³C NMR δ (ppm) (50 MHz): 10.6 (¹J_{Sn-C} = 350-333Hz), 13.6, 27.1 (³J_{Sn-C} = 60-58Hz), 28.8 (²J_{Sn-C} = 38Hz), 57.8, 76.2, 124.8 (²J_{Sn-C} = 36Hz), 165, 172