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A Convenient Synthesis of Protected E-enynals via Cross Coupling of Vinyltin Acetals with Bromoalkynes

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Key-words : Protected E-enynals, vinyltins, 1-bromoalk-1-ynes, cross-coupling.

Abstract: E-conjugated enynes bearing an acetal function on the allylic or the homoallylic position or/and on the propargylic or the homopropargylic position were conveniently obtained at room temperature in DMF via cross coupling of the corresponding vinyltins with 1-bromoalk-1-ynes in the presence of Pd^{II} catalysts.

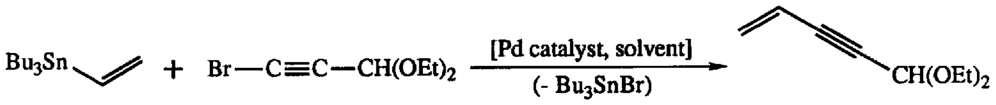
The synthesis of enynes has received special interest during the last 20 years and new methodologies using vinyl halides or vinyl organometallic compounds have been recently developed. The cross coupling of vinyl bromides, iodides and triflates with monosubstituted acetylenes has been achieved in the presence of a Pd^{II} catalyst using an amine as base, and more recently, these results have been improved by use of the couple Pd^{II}/Cu^{I} as catalyst, allowing cross coupling of acetylenes with vinyl chlorides[1-4].

The synthesis of enynes has been also performed using coupling of bromoalkynes with vinyl metals like vinyl boron[5], vinyl copper[6,7], vinyl zinc[8,9], vinyl aluminium[10] or vinyl magnesium reagents[11]. In this series, the higher compatibility with functional groups is observed with vinyl zinc reagents and a convenient way to obtain them is to transmetallate vinyl copper reagents with zinc dichloride[9].

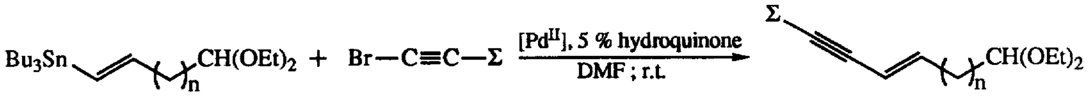
The use of organotin reagents to obtain enynes has been proposed by Stille and consists in a cross coupling of vinyl triflates or vinyl iodides with alkynyltins in the presence of palladium catalysts[12-15]. The interest of the method is a high tolerance for functional groups like allylic ethers, vinylic thioethers, esters or ketones[13,16,17]. Furthermore, the possible *in situ* generation of β-trimethylsilyl vinyl palladium iodides (using iodotrimethylsilane, $Pd(PPh_3)_4$ and alkynes) and their cross coupling with alkynyltins has been proved to be possible[18].

As we have recently studied different routes to obtain functional vinyltins with fixed configurations[19], we observed that the hydrostannation of 1-bromo-3,3-diethoxyprop-1-yne in the presence of $PdCl_2(PPh_3)_2$ according to Guibé[20] affords the expected E-vinyltin accompanied by (E)-1,1,6,6-tetraethoxy-hex-4-en-2-yne. This result demonstrates the possibility of a cross coupling between vinyltins and 1-bromoalkynes[21] and we have explored the possibilities of this system in order to obtain protected enynals, compounds of high potential interest for the synthesis of polyunsaturated compounds.

In a first step, the influence of the catalyst and of the experimental conditions on conversion rates was examined for the coupling of 1-bromo-3,3-diethoxy-prop-1-yne with vinyltributyltin.



Using $PdCl_2(MeCN)_2$ as catalyst after one hour at room temperature, conversion rates above 80 % were obtained whatever the nature of the solvent (DMF, THF, NMP, chloroform or benzene). Catalysts of the type $PdCl_2(PhCN)_2$, $PdCl_2(PPh_3)_2$ or $PdCl_2[P\text{-}(o\text{-}tolyl)_3]_2$ have also good efficiency but tetrakis(triphenylphosphine) palladium appears to be much less efficient and must be used in the presence of lithium chloride in order to obtain the desired products in reasonable yields. Due to the ability of the obtained enyne to polymerize, the reaction was conducted in the presence of hydroquinone (5 %). For further experiments on other substrates, hydroquinone has been systematically used and the reaction were conducted using $PdCl_2(MeCN)_2$ or $PdCl_2(PPh_3)_2$ as catalyst. Furthermore, (E)-1-tributylstannyl-3,3-diethoxy-prop-1-ene (**A**) and (E)-1-tributylstannyl-4,4-diethoxy-but-1-ene (**B**) easily obtained in high yields with a clean E configuration[19] were coupled with miscellaneous 1-bromoalk-1-ynes giving protected E-enynals often in good yields[22,23] (Cf Table I) :



A (n = 0) 3, 7, 9, 11, 13 (n = 0)

B (n = 1) Σ = Bu, Ph, COOMe, $CH(OEt)_2$, $CH_2CH(OEt)_2$ **4, 8, 10, 12, 14** (n = 1)

Due to the easy access to vinyltins with E configurations, this method complements the known methods for the obtention of Z-enynes[7,24,25] and furthermore, its high tolerance for the acetal function (and other functional groups) offers new possibilities for elongation or modification of the unsaturated skeleton. It is noteworthy that the acetal function can be introduced both by the bromoalkyne or by the vinyltin, leading to diprotected enynedials when the two moieties are bearing an acetal function (compounds **3**, **4**, **7**, **8**). In these unsaturated acetals the deprotection step has not been extensively studied, but primary observations demonstrate, as expected, an easy deprotection of the allylic acetals compared to the homoallylic ones. Furthermore the allylic acetal appears to be selectively deprotected in the presence of the propargylic acetal (this result has been obtained from **3** using wet silica gel[26]). In comparison with Stille's method, the high stability of the functional vinyltins **A** and **B**[27,28] compared with those of alkynyltins and the easy access to bromoalkynes[29,30] makes of the cross coupling between vinyltins **A** and **B** and bromoalkynes a convenient route to reach protected E-enynals and protected E-enynedials.

Acknowledgments

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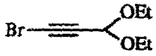
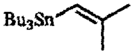
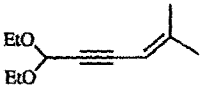
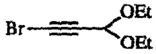
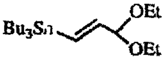
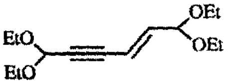
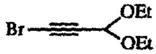
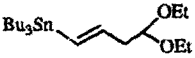
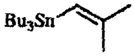
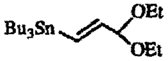
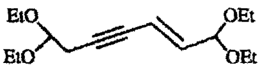
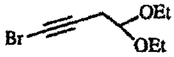
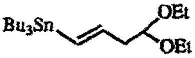
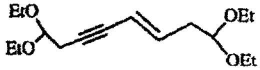
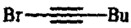
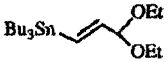
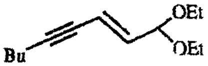
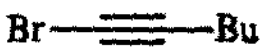
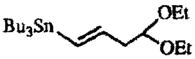
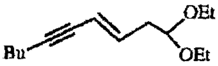
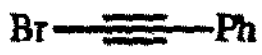
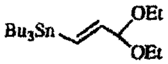
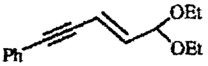
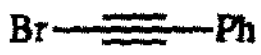
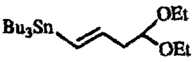
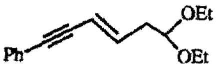
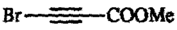
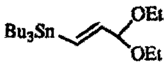
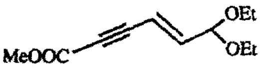
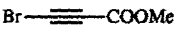
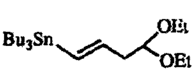
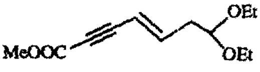
Table I : Synthesis of Protected Enynals via Cross Coupling of Vinyltins with Bromoalkynes in the presence of Pd^{II} Complex Catalysts

Bromoalkynes	Vinyltins	Experimental Conditions	Protected enynals	N°	Yield(a) %
		$PdCl_2(MeCN)_2$, 1h, 20° C		1	80
		$PdCl_2(MeCN)_2$, 1h, 0° C		2	63
		$PdCl_2(PPh_3)_2$,(b) 2h, 70° C		3	83
		$PdCl_2(MeCN)_2$, 4h, 20° C		4	67
		$PdCl_2(MeCN)_2$, 4h, 0° C		5	78
		$PdCl_2(MeCN)_2$, 9h, 0° C		6	44
		$PdCl_2(PPh_3)_2$, (c) 72h, 20° C		7	57
		$PdCl_2(PPh_3)_2$, 96h, 20° C		8	58
		$PdCl_2(PPh_3)_2$, 20h, 20° C		9	80
		$PdCl_2(PPh_3)_2$, 20h, 20° C		10	28
		$PdCl_2(PPh_3)_2$, 20h, 20° C		11	36
		$PdCl_2(PPh_3)_2$, 20h, 20° C		12	64
		$PdCl_2(PPh_3)_2$, 2h, 20° C		13	52
		$PdCl_2(PPh_3)_2$, 15h, 20° C		14	73

FOOTNOTES : a) Isolated yields after liquid chromatography on partially deactivated alumina (5 % H_2O) using a mixture hexane/ethyl acetate (98/2) as eluent. b) In this case the reaction has been conducted on neat reagents (without solvent). c) In this case, using $PdCl_2(MeCN)_2$ as catalyst, the coupling was less efficient and 1,1,6,6-tetraethoxy-hex-2,4-diene was obtained as a side product with 7 (diene / 7 = 20/80)[31].

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22. The vinyltins (2 mmoles) were reacted with one equivalent of bromoalkyne using DMF as solvent (10 ml) in the presence of palladium catalyst (3 mol %) and of hydroquinone (5 mol %).
23. The structures of compounds **1-14** were firmly established on the basis of physicochemical data (^{1}H n.m.r., ^{13}C n.m.r., IR and M.S.).
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