Highly General Stereo-, Regio-, and Chemo-selective Synthesis of Terminal and Internal Conjugated Enynes by the Pd-catalysed Reaction of Alkynylzinc Reagents with Alkenyl Halides

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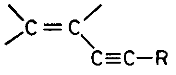
Summary The reaction of an alkynylzinc chloride, readily obtainable from the corresponding alkynyl-lithium and anhydrous zinc chloride, with an alkenyl iodide or bromide in the presence of a catalytic amount of a Pd–phosphine complex provides the corresponding terminal or internal enyne in high yield, the stereospecificity of the reaction being $\geqslant 97\%$.

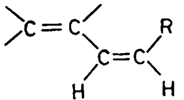
The conjugate enyne unit (**1**) is characteristic of a number of natural products, such as histrionicotoxin[1] (**2**) and laurencin[2] (**3**). It is also readily convertible into the corresponding conjugated diene (**4**) by known procedures.[3]



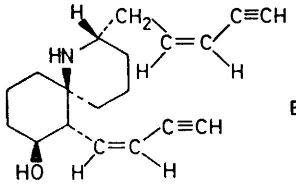
(1)

a, R = H

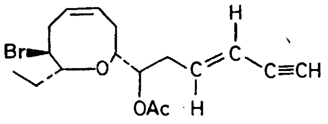
b, R = alkyl



(4)



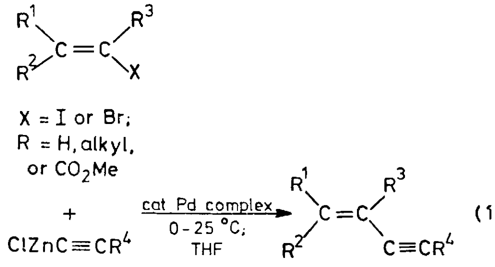
(2)



(3)

Despite various procedures developed recently for enyne synthesis,[4] certain types of enynes are not yet readily accessible in an efficient and selective manner. For example, none of the previous procedures[4] appears well suited for the direct and selective preparation of terminal enynes (**1a**) in high yields which does not involve any protection–deprotection sequence.

We now describe a stereo-, regio-, and chemo-selective procedure for the synthesis of both terminal and internal conjugated enynes which not only proceeds under very mild conditions but appears to be far more general than any of the previous methods. The method simply involves the reaction of an alkynylzinc chloride, readily obtainable by treating the corresponding alkynyl-lithium with 1 mol. equiv. of anhydrous zinc chloride dissolved in tetrahydrofuran (THF), with an alkenyl iodide or bromide in the presence of a catalytic amount (5 mol %) of a Pd catalyst [equation (1)]. The experimental results are summarized in the Table. The following observations indicate that alkynylzinc derivatives offer some distinct advantages over other alkynylmetal derivatives. First, the alkali metal derivatives of alkynes do not produce enynes under comparable conditions. Second, unlike ethynyl-lithium[5] and ethynylcopper[6] which readily disproportionate at or above room temperature, ethynylzinc chloride, readily obtainable by treating either commercially available ethynyl-lithium–ethylenediamine (Aldrich) or ethynyl-lithium generated at low temperature[5] with anhydrous zinc chloride, has been found to be sufficiently stable to disproportionation even at room temperature so that terminal enynes, essentially free from dienynes, can now be prepared for the first time in one step from the corresponding alkenyl halides and an ethynyl-lithium reagent. We expect this procedure to be directly applicable to the synthesis of a variety of natural products containing the terminal conjugated enyne unit. Third, all products have been formed without the concomitant production of other undesirable by-products, such as dienes and diynes, in any significant yield ($< 5\%$). Fourth, organozinc derivatives are known to be compatible with various electrophilic functionalities[7] which would be destroyed by the corresponding alkali metal and magnesium reagents, as exemplified by the preparation of methyl (*E*)-2-methyldec-2-en-4-ynoate (87%).



(5) (1)

Table. Preparation of conjugated enynes (**5**).[a]

R^1	R^2	R^2	R^4	X	Catalyst[b]	Yield[c] (%)
H	Bu^n	H	H	I	A	83 (65)
Bu^n	H	H	H	I	A	76 (71)
Bu^n	Et	H	H	I	A	70
H	Bu^n	H	$Pent^n$	I	A	82
Bu^n	H	H	$Pent^n$	I	A	87 (76)
Bu^n	H	H	$Pent^n$	I	B	82
Bu^n	Et	H	$Pent^n$	I	B	80
CO_2Me	Me	H	Bu^n	Br	A	87 (65)
CO_2Me	Me	H	Bu^n	Br	B	87

[a] To an alkynylzinc chloride in THF were added sequentially an alkenyl halide and a THF solution containing a Pd–phosphine complex (5 mol %) at 25 °C. After completion of the reaction, the mixture was treated with dil. aq. HCl, extracted with pentane, filtered through a short alumina column, and distilled. [b] A = $Pd(PPh_3)_4$; B = $Cl_2Pd(PPh_3)_2 + HAlBu^i_2$. [c] By g.l.c. Numbers in parentheses are isolated yields.

All reactions reported here are $\geqslant 97\%$ stereospecific (g.l.c.; ^1H and ^{13}C n.m.r.). Unlike in the diene synthesis *via* Pd catalysis reported by us recently,[8] $Pd(PPh_3)_4$[9] is as satisfactory as the previously employed Pd catalyst obtained by the reaction of $Cl_2Pd(PPh_3)_2$ with $HAlBu^i_2$. On the other hand, use of Ni–phosphine complexes, such as

$Ni(PPh_3)_4$, has resulted in the production of enynes in only low yields ($< 50\%$).

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