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Convenient One-Pot Synthesis of Functionalized Unsymmetrical (Z) or (E)-Enediynes From (Z) or (E)-1,2-Dichloroethylene. An Efficient Route to (Z,Z,Z) and (Z,E,Z)-Trienes

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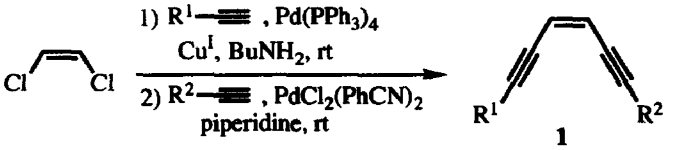
Abstract: *A variety of functionalized unsymmetrical (Z) or (E)-enediynes 1 and 2 are stereospecifically prepared in good overall yield by a simple straightforward one-pot procedure from (Z) or (E)-1,2-dichloroethylene and 1-alkynes. Zinc reduction of 1 and 2 leads efficiently to pure (Z,Z,Z) and (Z,E,Z) conjugated trienes.*

A new class of antitumor antibiotics (esperamicins, calicheamicins, dynemicin...)[1] has stimulated intense synthetic and mechanistic studies directed towards the 1,5-enediyne system which is at the origin of the biological properties of these substances.

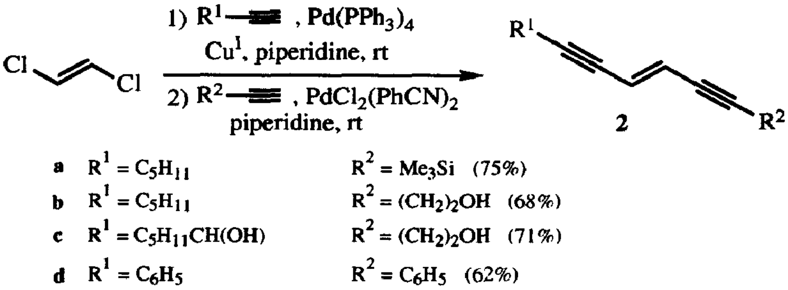
We have found that functionalized unsymmetrical (Z) or (E)-enediynes can be obtained in good overall yield by an experimentally straightforward one-pot procedure involving two sequential $Pd(PPh_3)_4$ and $PdCl_2(PhCN)_2$ catalyzed coupling reactions from (Z) or (E)-1,2-dichloroethylenes and 1-alkynes (schemes 1 and 2).



a	$R^1 = (CH_2)_4OH$	$R^2 = C_5H_{11}$ (73%)
b	$R^1 = C_5H_{11}$	$R^2 = Me_3Si$ (72%)
c	$R^1 = C_5H_{11}CH(OH)$	$R^2 = CH_2OH$ (72%)
d	$R^1 = (CH_2)_2OH$	$R^2 = CH_2OH$ (62%)
e	$R^1 = C(Me)_2NH_2$	$R^2 = C_5H_{11}$ (71%)
f	$R^1 = C(Me)_2NH_2$	$R^2 = C_5H_{11}CH(OH)$ (64%)

Scheme 1

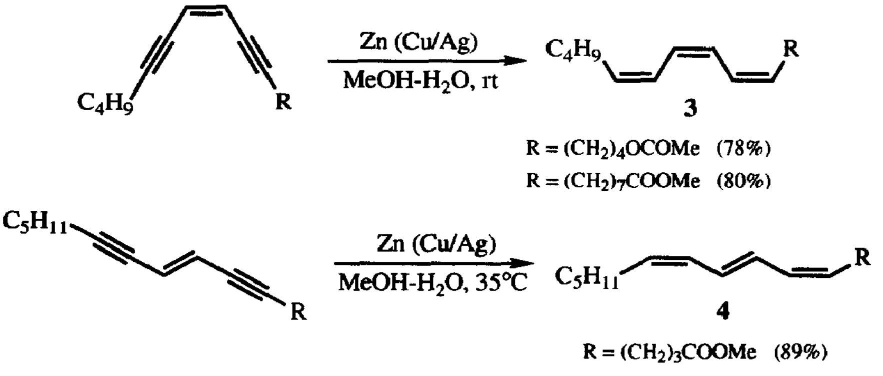
Unlike the case of the stepwise substitution of (E) and (Z)-dichloroethylenes[2,3] or the case of symmetrical disubstitution of (Z)-dichloroethylene,[4] where $Pd(PPh_3)_4$ can be used, it is noteworthy that the presence of $PdCl_2(PhCN)_2$[5] is essential for the efficiency of the one-pot cross coupling reaction. By using $Pd(PPh_3)_4$, instead of $PdCl_2(PhCN)_2$, lower yields were obtained (<10%).



	R^1	R^2
a	$R^1 = C_5H_{11}$	$R^2 = Me_3Si$ (75%)
b	$R^1 = C_5H_{11}$	$R^2 = (CH_2)_2OH$ (68%)
c	$R^1 = C_5H_{11}CH(OH)$	$R^2 = (CH_2)_2OH$ (71%)
d	$R^1 = C_6H_5$	$R^2 = C_6H_5$ (62%)

Scheme 2

(Z,Z,Z) and (Z,E,Z) conjugated trienes **3** and **4** were easily prepared in high yield by treatment of the (Z) and (E)-enediynes with activated zinc[6] in methanol-water under mild conditions (scheme 3):



$R = (CH_2)_4OCOMe$ (78%)
$R = (CH_2)_7COOMe$ (80%)

$R = (CH_2)_3COOMe$ (89%)
$R = (CH_2)_4OCOMe$ (91%)

Scheme 3

Typical procedure for the preparation of (7Z)-7-pentadecen-5,9-diyn-1-ol (1a):
To a solution of $Pd(PPh_3)_4$ (0.1 mmol, 116 mg), (Z)-1,2-dichloroethylene (4 mmol, 388 mg), $BuNH_2$ (4 mmol, 341 mg) and 5-hexyn-1-ol (2 mmol, 196 mg) in benzene (4 ml) was added CuI (0.2 mmol, 38 mg) at room temperature. The stirred reaction was kept at room temperature for 4 h and the volatile components were removed at reduced pressure (10 mmHg). Piperidine (5 ml), $PdCl_2(PhCN)_2$ (0.1 mmol, 39 mg) and 1-heptyne (2.4 mmol, 231 mg) were then added successively under an argon atmosphere. The stirring was continued until TLC analysis indicated complete consumption of the intermediate chloroenyne (generally 1-3 h). The reaction mixture was hydrolyzed with a saturated aqueous solution of ammonium chloride and extracted with ether. The organic extract was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by flash chromatography (petroleum ether / EtOAc : 70 / 30) afforded 320 mg (73%) of pure enediyne **1a**.[7]

References and notes

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7. Satisfactory spectral data were obtained for all new compounds.

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