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An Efficient Route to Skipped Diynes and Triynes, (Z,Z) Dienes and (Z,Z,Z) Trienes.

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Key Words: Copper(I) iodide; tetra-n-butylammonium chloride; skipped diynes and triynes; (1Z,4Z) dienes; (1Z,4Z,7Z) trienes.

Abstract: An efficient route to skipped diynes or triynes, (1Z,4Z) dienes or (1Z,4Z,7Z) trienes is described and illustrated by the synthesis of methyl 5Z,8Z,11Z eicosatrienoate.

Skipped (Z,Z) dienes and (Z,Z,Z) trienes constitute a partial structure of many natural and/or bioactive compounds such as, for example, the polyunsaturated fatty acids and the arachidonic acid metabolites.[1]

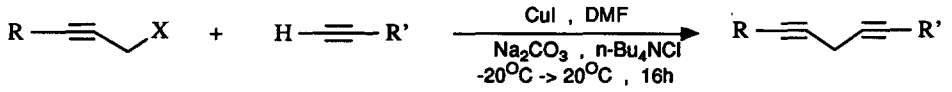
Different routes to these types of compounds or intermediates have been reported[1-5] but they very often involve copper(I)-catalyzed allylic or propargylic substitution of halides or tosylates by acetylenic Grignard reagents followed by stereoselective reduction of the triple bond.[1]

Direct propargylic substitution of halides by propargylic alcohols has been described in a water-dimethylsulfoxide mixture, in the presence of *ter*-butylamine and catalytic amounts of copper(I) salt.[6,7] Synthesis of β-diynes from propargylic halides and 1-alkynes, in a mixture of tetrahydrofuran and hexamethylphosphoramide, in the presence of copper(I) iodide and 1,5-diazabicyclo [4.3.0] non-5-ene (or 1,8-diazabicyclo [5.4.0] undec-7-ene) has also been reported.[8]

We wish to report an alternative efficient procedure for preparing the skipped diynes.

We have recently reported that a direct allylic substitution of allylic halides by 1-alkynes can be conveniently and efficiently performed in the presence of sodium or potassium carbonate and catalytic amounts of copper iodide and tetra-n-butylammonium chloride, without formation of an acetylenic Grignard intermediate.[9]

We now report that treatment of propargylic halides or tosylates with 1-alkynes, in the presence of copper(I) iodide, sodium carbonate and tetra-n-butylammonium chloride, in N,N-dimethylformamide or acetonitrile, leads to high yields of skipped diynes (Scheme 1). The beneficial effect of tetraalkylammmonium chloride on the reaction yields has been observed both in N,N-dimethylformamide and in acetonitrile, the effect being more pronounced in acetonitrile (Table).

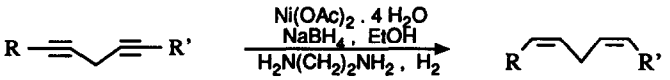


Scheme 1

The reaction is highly chemo and regioselective: functionalized skipped diynes can be prepared without protection and deprotection of the functional groups and are formed without isomeric allenes. It also appears general being applicable to various 1-alkynes and various propargylic tosylates and halides (chlorides, bromides or iodides) (Table).

The described procedure, by its regioselectivity as well as its generality and its operational simplicity, compares well with the previously described direct propargylic substitution by 1-alkynes.[6,7,8]

Stereoselective partial reduction[10] of the so obtained β-diynes has efficiently led to skipped (Z,Z) dienes (Scheme 2) or to skipped (Z) enynes after subsequent desilylation (scheme 3).



	R	R'	Isolated yield (%) [11]
	C_5H_{11}	C_5H_{11}	79
	C_5H_{11}	$(CH_2)_3COOMe$	70
Scheme 2	C_8H_{17}	CH_2OH	90

	R'	Isolated yield (%) [11]
	C_5H_{11}	91
Scheme 3	$(CH_2)_3COOMe$	77

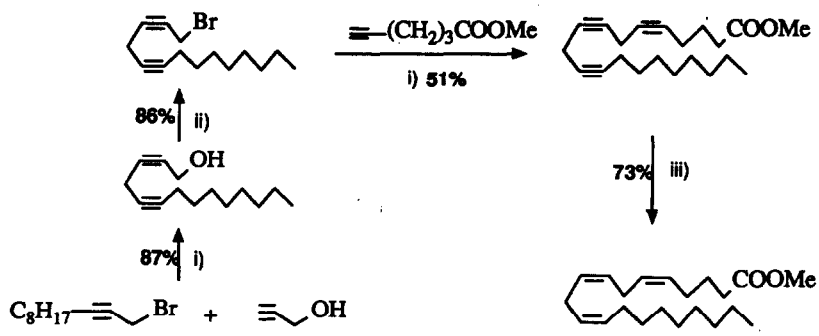
An efficient chain elongation to skipped triynes which leads to (1Z,4Z,7Z) trienes by semi-reduction, has been illustrated by the synthesis of methyl 5Z,8Z,11Z eicosatrienoate[12,13] (Scheme 4).

In summary, an efficient synthetic methodology to skipped diynes and triynes, (1Z,4Z) dienes and (1Z,4Z,7Z) trienes has been developed. It should be extendable to skipped polyenes and should be of great value by its chemo, regio and stereoselectivity as well as its convenience. Its application in the synthesis of arachidonic acid metabolites will be reported in due course.

Table: Chemo and regioselective synthesis of skipped diynes from propargylic halides (or tosylates) and 1-alkynes (scheme 1). [a]

Entry n°	R	R'	X	Product [b]	Yield(%) [c]
1	Me_3Si	C_5H_{11}	Br	Me_3Si—≡—≡—C_5H_{11}	(91) [d]
2	"	"	"	" "	traces [d], [e]
3	"	"	"	" "	70 (87)
4	"	"	"	" "	55 (64) [e]
5	Et	$(CH_2)_2CO_2Me$	I	Et—≡—≡—$(CH_2)_2CO_2Me$	78 [d]
6	Et	"	I	" "	82
7	Et	"	OTs	" "	76
8	Me_3Si	$(CH_2)_3CO_2Me$	Br	Me_3Si—≡—≡—$(CH_2)_3CO_2Me$	75
9	C_5H_{11}	"	Br	C_5H_{11}—≡—≡—$(CH_2)_3CO_2Me$	73
10	Me_3Si	$CH(OH)(CH_2)_4CH_3$	Br	Me_3Si—≡—≡—$CH(OH)(CH_2)_4CH_3$	75
11	"	CH_2OH	Br	Me_3Si—≡—≡—CH_2OH	61
12	Et	"	OTs	Et—≡—≡—CH_2OH	76
13	"	"	I	" "	84
14	"	$(CH_2)_4OH$	OTs	Et—≡—≡—$(CH_2)_4OH$	70

a) Mixtures in DMF of propargylic halides or tosylates (1.1 equiv.), 1-alkynes (1 equiv.), CuI (1 equiv.), n-Bu_4NCl (1 equiv.), Na_2CO_3 (1.5 equiv.), were mixed at -20°C and stirred overnight at room temperature unless otherwise noted ; b) Ref 11 ; c) Isolated yields , GLC yields are in parentheses ; d) Reaction performed in acetonitrile ; e) Reaction performed in the absence of n-Bu_4NCl .



Scheme 4 i) CuI (1 equiv.), n-Bu_4NCl (1 equiv.), Na_2CO_3 (1.5 equiv.), DMF, -15°C -> 20°C, 23h ; ii) CBr_4 (1.3 equiv.), PPh_3 (1.4 equiv.), CH_2Cl_2 0°C, 1.5h ; iii) $Ni(OAc)_2.4\,H_2O$, $NaBH_4$, EtOH, $H_2N(CH_2)_2\,NH_2$, H_2

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