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COPPER(I) AND PHASE TRANSFER CATALYSED ALLYLIC SUBSTITUTION BY TERMINAL ALKYNES

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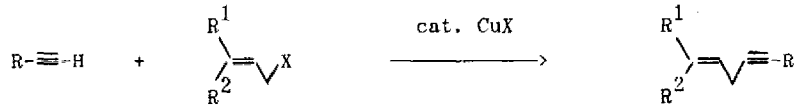
Summary: The Cu(I) catalysed allylic substitution of (un)substituted allyl halides by alk-1-ynes can proceed smoothly at or near room temperature under solid-liquid phase transfer conditions.

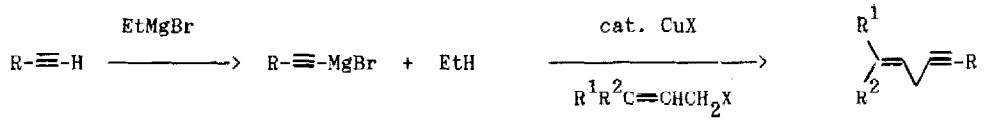
Allyl substituted acetylenic compounds are often involved as intermediates in organic synthesis [1]. The skipped 1,4 enyne moiety can also be found in natural[2] and/or bioactive[3] compounds.

Direct allylic substitution of allylic halides by terminal alkynes in the presence of a catalytic amount of a copper(I)salt (scheme 1) have been reported [4,5,6,7] although this type of reaction is generally restricted to unsubstituted allyl halides ($R^1 = R^2 = H$) and performed under heating, except for alk-1-ynols.[6]



Scheme 1

The reaction is more general and proceeds more efficiently under much milder conditions by prior conversion of the 1-alkyne into the alkynyl magnesium halide [8] (Scheme 2).

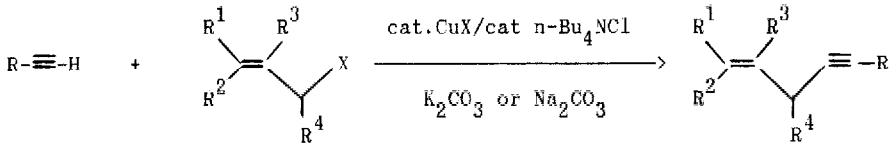


Scheme 2

This latter method is more widely used in organic synthesis but it generally needs protection of functional groups thus limiting the extent of the synthetic application.

We have recently described a copper(I) and phase-transfer catalysed iodination of terminal alkynes [9] and the tolerance towards functionalities is one of the advantages of this procedure.

We wish to report herein that the same catalyst system (cat.CuX/cat.nBu_4NCl/K_2CO_3 or Na_2CO_3) can be efficiently used for the direct allylic substitution by terminal alkynes (Scheme 3). Indeed, good yields of allyl substituted acetylenic compounds are obtained at or near room temperature, in N,N dimethylformamide, by reaction of allyl halides with alk-1-ynes, in the presence of potassium or sodium carbonate and catalytic amounts of a copper(I) salt and tetra-n-butylammonium chloride (Scheme 3 and Table).

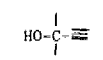
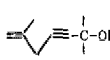
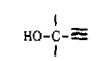
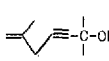
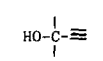
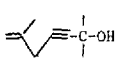
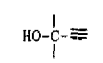
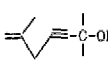
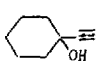
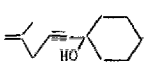
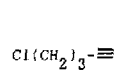
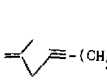
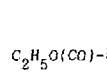
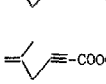
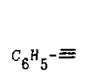
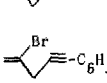
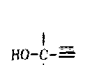
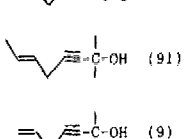
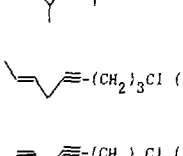


Scheme 3

Control reactions verify the necessity of having the copper(I) catalyst (either chloride or iodide) in the reaction mixture. Modifying the conditions by addition of tetra-n-butylammonium chloride, even in catalytic amounts, greatly enhances the reaction rate. Under the described conditions the coupling of allylic halides with terminal alkynes proceeds smoothly at or near room temperature with various alk-1-ynes. The compatibility of the described procedure with a number of functional groups is illustrated by the results shown in the Table. The same mild conditions can be applied even in the case of substituted allyl halides. The regioselectivity of the carbon-carbon bond formation towards the allylic moiety, when involved, is relatively high compared to the literature.

Typically, a reaction can be very conveniently run as follows. The allyl halide (1 equivalent) was added at room temperature under an inert atmosphere to a well-stirred suspension in DMF of alk-1-yne (1.1 equivalent), potassium or sodium carbonate (1.5 equivalent), tetra-n-butylammonium chloride (0.1 equivalent) and a copper(I) salt (0.05 equivalent). Stirring was continued for 6 to 48h. Ether was then added to the reaction mixture. After filtration through a bed of celite, the organic phase was washed with brine, dried over magnesium sulphate and the solvent evaporated under reduced pressure. Purification by flash chromatography on silica gel gave the pure product.

Table: Cu(I) and phase transfer - catalysed direct allylic substitution of allyl halides by alk-1-ynes [a].

Alk-1-yne	Allyl halide	Temp (°C)	Time (h)	Product [b]	Yield [c] (%)
		r.t	24 [d]		0
		r.t	6 [e]		38
		r.t	6		76
		r.t	16		88
		r.t	16		95
		r.t	24 [f]		92
		0	16		90
		40	4		75
		0	24		90 [g]
		r.t	24		83 [g]
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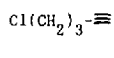
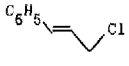
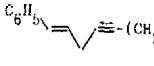
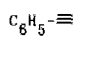
		40	4	 [h]	90
		40	2		78 [g][i]

a) Reactions were carried out under an inert atmosphere, in DMF with allyl halide (1 equiv.), terminal alkyne (1 to 1.1 equiv.), K_2CO_3 or Na_2CO_3 (1.5 equiv.), n-Bu_4NCl (0.1 equiv.) and CuI (0.05 equiv.); b) All compounds were characterized by mass spectra and/or coupled glc-mass spectra, i.r, ^1H and ^{13}C n.m.r data; c) Yield of isolated product; d) No copper(I) salt was added; e) No n-Bu_4NCl was added; f) CuCl was used instead of CuI; g) The isomeric purity was determined by g.l.c on capillary columns; h) ref.10 ; i) The isomeric purity is $\geqslant$ 95%.

The present procedure appears to be quite efficient for a direct use of terminal alkynes in the allylic substitution of allyl halides. The relatively high conversion and regioselectivity, the tolerance towards functionalities combined with the mild conditions and the simplicity of the operation should make it potentially very useful in the synthesis of skipped 1,4 enynes[11] and skipped 1,4 dienes[12] as stereocontrolled reduction of the triple bond is well-known.[1c]

References and Notes

(1). For recent examples see: a) B. Anorbe, V.S. Martin, J.M. Palazon and J.M. Trujillo, Tetrahedron Lett. (1986), 4991; b) W.J. Dejarlais and E.A. Emken, Lipids,(1986), 21, 662 (Chem. Abstr., 1987, 107, 023125); c) C.A. Henrick, Tetrahedron (1977), 33, 1845 and references cited therein.

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(6). A. Sevin, W. Chodkiewicz and P. Cadiot, Tetrahedron Lett., (1965), 1953; Bull. Soc. Chim. Fr., (1974), 913.

(7). M. Bourgain and J.F. Normant, Bull. Soc. Chim. Fr., (1969),2477.

(8). a) W. Ziegenbein in "Chemistry of Acetylenes"; H.G. Viehe Ed.; Marcel Dekker, New York (1969), p.169 and references cited; b) V. Jäger and H.G. Viehe in "Methoden der Organischen Chemie", Houben-Weyl, E. Müller Ed., Band V/2a (1977), p.463 and references cited.

(9). T. Jeffery, J. Chem Soc., Chem. Commun., (1988), 909.

(10).This type of 1,4 pentenyne link between two aromatic rings can be found in the structure of rooperol and its derivatives which are anticancer agents[3a].

(11).Terminal or (E) enynes.

(12).Terminal (E) or (Z) dienes or (E,E) or (E,Z) dienes.

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