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COPPER CATALYSED PREPARATION OF VINYL ETHERS FROM UNACTIVATED VINYLIC HALIDES

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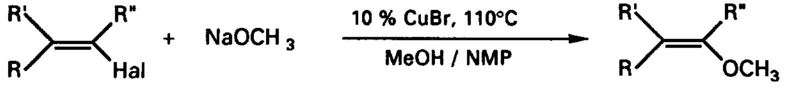
Abstract: Vinylic halides have been treated with sodium methoxide in the presence of 10 mol% of copper bromide. Most of the vinylic methyl ethers could thus be obtained in a good yield. The reaction proceeds with a 100% retention of configuration. The mechanism of the process is shortly discussed.

INTRODUCTION

Nucleophilic vinylic substitutions in vinylic halides have been studied extensively in the past.[1] As it appears from the cited reviews by far most of the vinylic halides investigated were activated by electron withdrawing groups to make them suitable to undergo a substitution reaction. Only a few examples are known in which the halide of unactivated substrates are substituted. To achieve substitution in unactivated halides, polar non-protic solvents[2,3] or catalysis by a transition metal compound, containing nickel,[4,5,6] palladium,[4,5] or copper[7,8,9] is required. In the case of copper, however, stoechiometric amounts are generally required.

The transition metals nickel and palladium are not capable of catalysing the substitution in an aromatic or vinylic halide by an *alkoxide*.[10] Whitesides *et al.*[11] used a stoechiometric amount of a copper compound to achieve the alkoxydehalogenation of a non-activated vinylic halide. They applied a copper(I) alkoxide as a nucleophile in the substitution of 1-bromocyclohexene and obtained the corresponding vinyl ether. The low yield and the laborious preparation of the copper alkoxide make this method rather intricate for the preparation of vinyl ethers.

In nucleophilic *aromatic* substitution copper(I) bromide turned out to be a good catalyst for alkoxydehalogenations.[12,13] Recently, we improved this method so that it became applicable to all types of aromatic and heteroaromatic halides.[14]



(1)

1a-13a

R : alkyl, thiomethyl, or hydrogen.
R': alkyl, phenyl.
R": alkyl, phenyl, hydrogen

1b - 13b

The work presented in this paper shows that this procedure, in which only 10 mol% of catalyst is needed, could be applied to vinylic halides as well. We have examined the scope of the reaction with respect to several vinylic halides. Furthermore, the mechanism of the reaction and of side-reactions observed, are described.

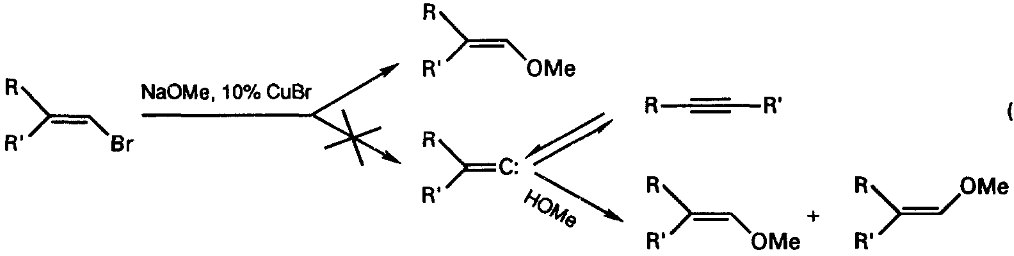
RESULTS

The results of the reactions studied are summarized in table 1. Most of the vinyl ethers prepared, could be isolated in reasonable yields. The reaction conditions were mild and the reaction times short when a high base concentration (4.6 mol/l) was used. To reduce the reaction time a polar non-protic solvent, namely *N*-methylpyrrolidinone (NMP) was used. Such a solvent can also be responsible for a reductive dehalogenation as was found before, when heteroaromatic halides were used.[14] Vinylic bromides, however, turned out not to be very sensitive to this side-reaction. In the reactions investigated relatively small amounts (less than 10 mole %) of this side-product were observed. Overall, the reaction proved to be well applicable to a significant number of substrates such as bromo- and iodocycloalkenes (**1a-4a**), or non-cyclic vinylic bromides (**6a-10a**). The reaction proceeded with retention of configuration (**9*E*/*Z*, 10*E***) which gives this method an advantage over non-catalysed vinylic substitution reactions in which partial inversion is often observed (see the cited reviews: ref 1). Chlorine, which is usually much less reactive in copper-catalysed substitution reactions[12a] could be substituted as well, though more reduction and dimerisation occurred. In absence of the catalyst no reaction, nor side-reaction occurred.

Serious side-reactions of the non-catalysed nucleophilic vinylic substitution are α- and β-eliminations with formation of alkynes or carbenes. We have investigated the occurrence of these undesired processes under our catalytic conditions.

α-Elimination

The possibility of α-elimination was examined for substrates **6a-10a** that can, in principle, undergo such an elimination, having a hydrogen situated geminal to the halogen (compare ref. 1b). However, in none of the cases any elimination-product was traced and the substitution products were isolated in good yields. Additional support for the absence of such an elimination is the observation of retention of configuration in the reactions of compounds **9** and **10** (compare eq. 2).

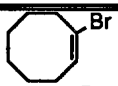
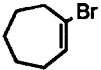
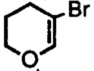
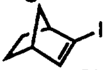
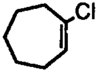
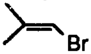
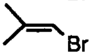
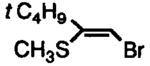
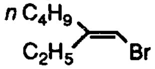
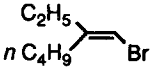
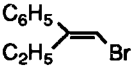
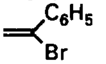
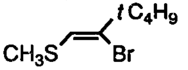
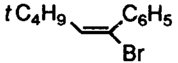
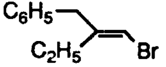
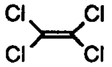


(2)

β-Elimination

As has been observed in non-catalysed reactions,[1] substrates in which a proton and the leaving group are in *trans* position may undergo β-elimination. When α-bromostyrene, **11a** was added to the reaction mixture containing base in a high concentration, β-elimination occurred immediately, and phenylethenylcopper precipitated from the solution, thus consuming the catalyst.

Table 1 - Results of the vinyl ether synthesis.

no	substrate	T (°C)	t (min.)	Isolated Yield (%)	Remarks
1		85	60	70	
2		110	5	65	
3		110	90	82	
4		30-70	90	60	a
5		110	60	40	
6		80	240	40	b
		110	240	65	c
8*Z*		120	180	70	d
9*E*		110	75	90	e
9*Z*		110	75	96	f
10*E*		110	60	85	e
11		80	-		g
12*Z*		110	-		g
13		110	60	50	d
14		110	60		h
15		80	120		i

a: 18% of reductive dimerisation took place. Dimer isolated as a mixture of diastereomers b: less than 10% of side-products were detected; low yield presumably due to losses of the volatile product. c: sodium *n*-butoxide used (product 7b) d: configuration suggested based on retention of configuration observed with substrates 9 and 10. e: product pure *E*-configuration, based upon NMR-data in experimental part. f: product pure Z-configuration, based upon NMR-data in experimental part. g: β-elimination of substrate, acetylene was the only product isolated h: several products detected. i: freshly prepared sodium ethoxide used as base; very small amounts of ethyl ether detected.

The formation of the acetylene proceeded so much faster than the substitution process that the latter was not able to compete effectively with the elimination reaction. In the case of vicinally disubstituted vinylic bromides sensitive to β-elimination we hoped some substitution to occur, because in that case the catalyst would not be converted into an insoluble acetylide. In the reaction with (*Z*)-2-bromo-3,3-dimethyl-1-

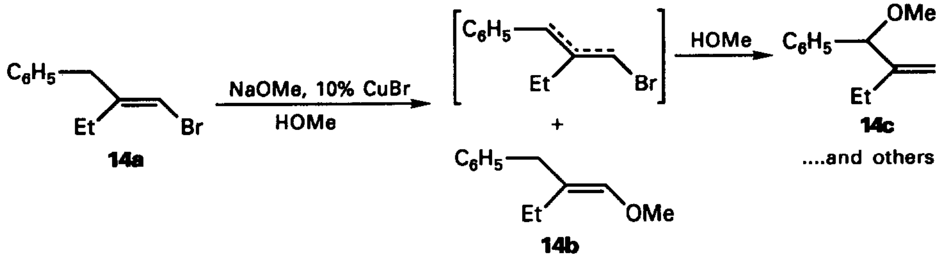
methylthio-1-butene, **12a**, however, 1-methylthio-3,3-dimethylbutyne was the only product observed. So the rate of the elimination is significantly higher than that of substitution, even when the copper catalyst remains available.

Actually, the choice of **12a** for studying the competition between substitution and β-elimination is not satisfactory, since the RS-group has a rate-decreasing effect upon the substitution. This effect was experienced in the case of 1-bromo-2-methylthio-3,3-dimethyl-1-butene, **8**: in spite of raising the reaction temperature to 120°C, full conversion took 3 h. Unfortunately, more suitable substrates were not available. (The accessibility of the substrates is described in ref. 15.)

As substrates in which the hydrogen and the bromide are situated *cis* normally are less sensitive to β-elimination,[1] the competition of substitution and β-elimination was examined with 1-bromo-3,3-dimethyl-1-phenyl-1-butene, **13a**. Using this substrate substitution indeed appeared to be the predominant process. No elimination was observed and the aimed product was isolated in a 50% yield.

Acidic vicinal protons

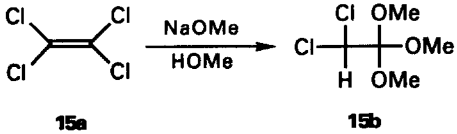
When a vinylic halide was used containing an acidic proton adjacent to the double bond another side-reaction occurred. Treatment of substrate **14a** with base under the standard reaction conditions gave seven products with a molar mass of 176. This mass corresponds with that of the aimed substitution product. The composition of the product mixture, containing traces of compound **14c** among others, suggests an attack of one of the benzylic protons by the base leading to the formation of an intermediate in which the double bond is able to shift, followed by an addition of the alcohol (equation 3). Furthermore this intermediate provides the possibility of a partial inversion of configuration of the double bond in the products to occur.



(3)

Tetrachloroethene

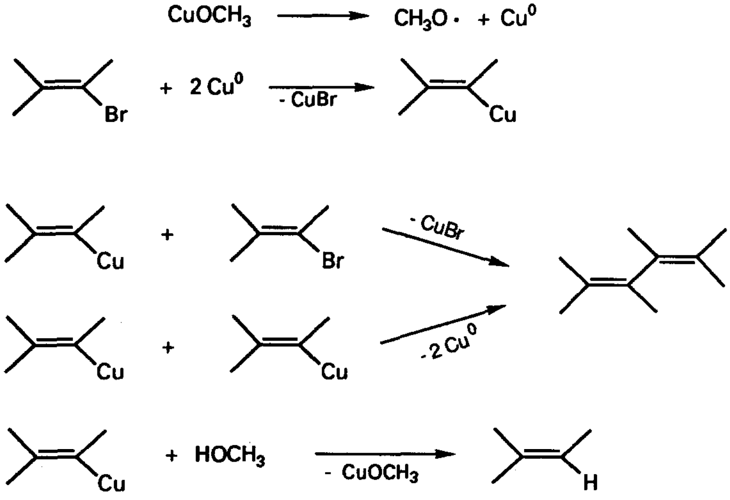
When tetrachloroethene, **15a** was treated with sodium methoxide, even in absence of CuBr a vigorous reaction occurred and a gas evolved. Analysis of the reaction mixture showed the presence of ~ 20 mol% of 1,1-dichloro-2,2,2-trimethoxyethane (**15b**)(eq. 4). No other products were detected. This product is probably formed by the substitution of two chlorine atoms, followed by addition of methanol. The structure of the volatile product is not elucidated yet.



(20%) (4)

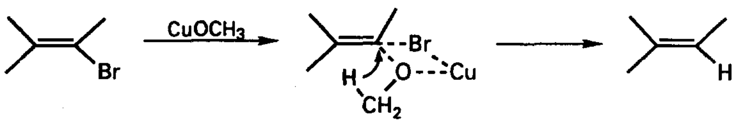
Other side-reactions

During our research alkenes and dimers were observed in relatively small amounts (less than 15 %). This side-reaction appeared to be copper mediated, as it did not occur in absence of the catalyst. A route to these side-products could involve a vinylcopper intermediate.[16,17,18] In our reaction mixtures a vinylcopper species can be formed from a reaction of the vinylic halide and Cu(0).[18] The latter arises from the thermal decomposition of copper methoxide (scheme 1).[11] The freshly formed copper(0) is very reactive, but looses part of its reactivity when copper clusters are formed.



Scheme 1 - Reductive dehalogenation and dimerisation

An additional mechanism for the reductive dehalogenation is depicted in equation 5. It is based upon our results in the corresponding aromatic substitution reaction.[14] During these investigations we found that major part of the protons in the reduced side-product were delivered by the α-carbon, whereas the alkene formation from a vinyl copper species (scheme 1) involves a hydroxyl proton.

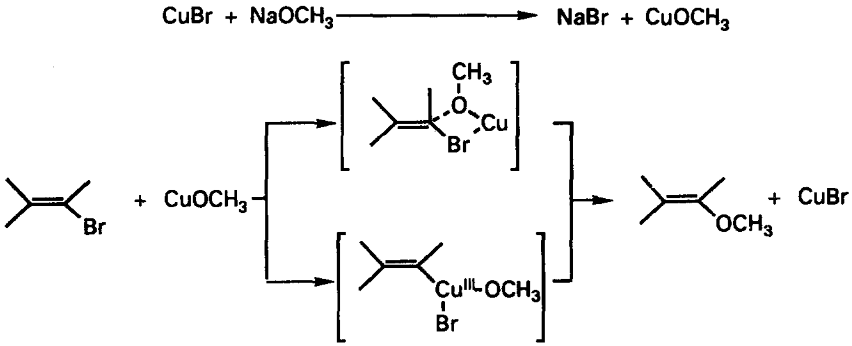


(5)

MECHANISM OF THE SUBSTITUTION REACTION

Although in non-catalysed nucleophilic vinylic substitutions various mechanisms have been proposed,[1] much less pathways have been postulated when in these processes a copper catalyst is applied. The known catalysed routes involve a four-centre transition state[9,19] or a copper(III) intermediate (scheme 2).[20,21] Elimination-addition[22] or electron-transfer processes, involving radical intermediates[23] were hitherto only mentioned in the case of nickel- and palladium-catalysed reactions.[24]

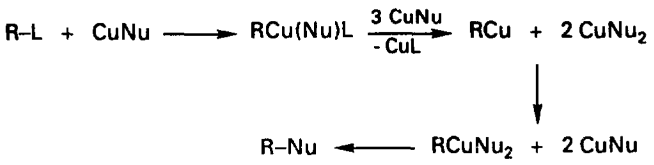
In practice the mechanisms are hard to discern, because of a lack of experimental data. The results found here add some details, which could be useful for further illucidation of the mechanism.



Scheme 2 - Possible mechanisms of the substitution reaction

Firstly, we observed a 100% retention of configuration in this reaction. This observation excludes the elimination-addition mechanism mentioned,[22] since this pathway is not fully stereospecific, but prefers the *cis*-isomer. A radical intermediate becomes unlikely for a comparable reason, since also here some inversion of configuration is usually observed.[17,18]

Secondly, the observed dimerisation could give additional information with respect to the reaction mechanism, as this process is believed to occur via a vinyl copper(I) intermediate.[18] This shows that these species could exist in our reaction mixture,[25] and can play an intermediary role in the reaction. A mechanism as proposed by Cohen *et al.*[20] thus becomes possible (eq. 6).[26] This mechanism also involves a copper(III) intermediate.



$$\begin{tikzcd}[column sep=small] \text{R–L} + \text{CuNu} \arrow[r] & \text{RCu(Nu)L} \arrow[r, "3\,\text{CuNu}", "-\,\text{CuL}"'] & \text{RCu} + 2\,\text{CuNu}_2 \arrow[d] \\ & \text{R–Nu} & \text{RCuNu}_2 + 2\,\text{CuNu} \arrow[l] \end{tikzcd} \qquad (6)$$

However, the vinyl copper(I) intermediate can also be formed from copper(0) and the vinylic halide as shown above (scheme 1). This indicates that the aimed product and the dimer can be formed via independent pathways. For this reason both the copper(III) mediation and the four-centre mechanism are still possible (scheme 2). They are indiscernible on the basis of the available experimental data.

EXPERIMENTAL SECTION

General

In all reactions an atmosphere of inert gas (N_2) was maintained. Solvents were dried, and distilled prior to use, and, as the reagents stored under nitrogen. All chemicals were commercially available, unless stated otherwise. 1-Bromocyclooctene[**1a**],[27] 1-bromocycloheptene[**2a**],[28] 1-iodonorbornene[**4a**][29], 1-chlorocycloheptene[**5a**],[28] 1-bromo-2-methyl-1-propene[**6a**],[28] α-bromostyrene[**11a**],[28] 2-benzyl-1-bromo-1-butene[**14a**][30], *E*- and Z-1-bromo-2-ethyl-1-hexene[**9a**],[30] 1-bromo-2-phenyl-1-butene[**10a**],[30] and 1-bromo-1-phenyl-3,3-dimethyl-1-butene[**13a**][31] were prepared as described in the literature. 3-Bromo-5,6-dihydro-4H-pyran[**3a**] was prepared as described below. The vinylic bromides containing a methylthio functionality[**8a**,**12a**] were prepared using the literature method for the corresponding vinylic chlorides.[32]

Analyses

Reactions were monitored by taking samples of the reaction mixture through a serum cap with syringe techniques. The samples were then added to a mixture of water and diethyl ether. The organic layer was analysed quantitatively by GLC on a Pye Unicam 104 gas chromatograph using a capillary silica-coated column. The GC-MS analysis were carried out on a Varian E-4 mass spectrometer or a Kratos GC-MS combination. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer (^1H: 200 MHz, ^{13}C: 50 MHz) using deuteriochloroform as a solvent and internal standard, unless mentioned otherwise.

3-Bromo-5,6-dihydro-4H-pyran, 3a: In a 500-mL three-necked round-bottomed flask, equipped with a thermometer, a dropping funnel, and a magnetic stirrer, 22 g (0.26 mol) of 3,4-dihydro-2H-pyran was dissolved in 100 mL CH_2Cl_2, and 40 g (0.25 mol) of bromine was added in 30 min at 3 to 5°C. When the addition was complete, the dropping funnel was removed, after which the solvent and the remaining starting material were removed *in vacuo.*

In the same flask 0.5 mol of *N,N*-diethylaniline was added to the 5,6-dibromo-3,4-dihydro-2H-pyran formed and the mixture was heated to 100°C for 30 min until it became solid. The reaction mixture was cooled to room temperature and 200 mL of pentane was added. The mixture was washed with 5 portions of 50 mL 1 M. aqueous HCl in order to remove the base. The combined acidic layers were extracted twice with small portions of pentane. The combined organic layers were subsequently concentrated *in vacuo* and the product was isolated by distillation. Yield 32.8 g (80%). Physical data are described in table 2.

(Z)-2-Bromo-1-methylthio-3,3-dimethyl-1-butene, 12a: In a 250-mL three-necked round-bottomed flask, equipped with a thermometer, 0.2 mol of methanesulphenyl bromide was prepared by adding 16 g (0.1 mol) bromine to 18.8 g (0.1 mol) methyl disulphide in 75 mL CH_2Cl_2 at -30°C. To this solution 8.2 g (0.1 mol) *tert.*- butylacetylene was added and the mixture was stirred for 6 h at room temperature. The mixture was washed with 75 mL of water after which the water layer was extracted twice with 25 mL of pentane. The combined organic layers were concentrated *in vacuo* and the product was obtained by distillation in a 50% yield (10.5 g). Physical constants are listed in table 2.

(Z)-1-Bromo-2-methylthio-3,3-dimethylbutene, 8a: In a 500-mL three-necked round-bottomed flask, equipped with a thermometer, a reflux condenser, and a dropping funnel, 16.4 g (0.2 mol) of *tert.*- butylacetylene was dissolved in 200 mL of ethyl acetate. The solution was cooled to 0°C and 25.4 g (0.2 mol) of methanesulphenyl bromide in 75 mL CH_2Cl_2 was added over a period of 30 min. The reaction mixture was washed with water after which the water layer was washed twice with pentane. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The product was isolated by distillation in a 80% yield (33.4 g). Physical data are described in table 2

A typical procedure for the bromine substitution: In a 100 mL three-necked-flask, equipped with a thermometer, a reflux condenser and a septum, 4.1 g (75 mmol) of sodium methoxide was suspended in 12 mL of NMP and 3 mL of methanol under magnetic stirring. Subsequently, 50 mmol of the haloalkene and 0.72 g (5 mmol) copper(I) bromide[33] were added and the reaction mixture was treated under the conditions as described in table I. When the GLC monitoring showed that the reaction had finished the reaction mixture was cooled down, 75 mL of an aqueous 5% NaCN solution was added and the mixture was extracted with 5 portions of 25 mL of diethyl ether.[34] The combined organic layers were dried ($MgSO_4$), the solvent was distilled of and the product was isolated by distillation. The yields are given in table 1 and physical data of the products in table 2.

Table 2 - Physical data of products.

no.	Compound	bp°C (mm Hg); n_D^{20}	^{1}H-NMR (ppm); (coupl.const in Hz)	^{13}C-NMR (ppm)
3a	3-bromo-5,6-dihydropyran	62-63 (20)	1.93 (2H, tt: ^3J= 10.3, ^3J= 6.4); 2.34 (2H, td: ^3J= 6.4, ^4J= 1.6); 3.91 (2H, t: ^3J= 10.3); 6.57 (1H, t: ^3J= 1.6)	23.7; 29.1; 64.7; 98.8; 143.0
8a	(Z^a)-1-bromo-2-methylthio-3,3-dimethyl-1-butene	74-76 (15)	1.16 (9H, s); 2.29 (3H, s); 6.62 (1H, s)	18.4; 28.6; 41.2; 112.2; 152.7
12a	(Z^a)-2-bromo-1-methylthio-3,3-dimethyl-1-butene	85-90 (15)	1.14 (9H, s); 2.28 (3H, s); 6.19 (1H, s)	16.4; 29.3; 39.7; 124.9; 134.6
9*E*a	(*E*^{b})-1-bromo-2-ethyl -1-hexene	ref 30	0.88 (3H, t: 6.0); 0.97 (3H, t: 7.5); 1.2-1.5 (4H, m) ; 2.13 (2H, t: 7.2); 2.24 (2H, q: 7.5); 5.82 (1H, s)	11.5; 13.8; 22.3; 25.8; 29.7; 35.3; 100.2; 147.1
9Za	(Z^b)-1-bromo-2-ethyl -1-hexene	ref 30	0.88 (3H, t: 6.5); 0.97 (3H, t: 8); 1.2-1.5 (4H, m); 2.13 (2H, q: ^3J= 8.0); 2.24 (2H, t: 6.2); 5.86 (1H, s)	12.4; 13.9; 22.6; 29.1; 29.3; 32.5; 100.5; 147.2
1b	1-methoxycyclooctene	85 (35)	1.36-1.56 (8H, m); 1.97-2.10 (2H, m); 2.10-2.22 (2H, m); 3.43 (3H, s); 4.42 (1H, t: ^3J= 8.3)	25.0; 26.25; 26.34; 28.4; 29.6; 31.1; 53.9; 94.3; 158.3
2,5b	1-methoxycycloheptene	53 (15)	1.38-1.58 (4H, m); 1.58-1.74 (2H, m); 1.97-2.08 (2H, m); 2.16-2.25 (2H, m); 3.38 (3H, s); 4.66 (1H, t: ^3J= 7.0)	25.3; 25.6; 28.2; 32.2; 33.7; 54.0; 96.0; 162.0
3b	3-methoxy-5,6-dihydro-4H-pyran	153	1.73-1.84 (2H, dd: ^3J = 5.1, ^3J= 6.4); 2.07 (2H, t: ^3J= 6.4); 3.36 (3H, s); 3.69 (2H, t: ^3J= 5.1); 6.07 (1H, s)	22.1; 23.2; 54.6; 64.8; 124.4; 140.7
4b	1-methoxynorbornene	45-50 (20); 1.4683	0.96-1.06 (1H, m); 1.06-1.20 (2H, m); 1.38-1.49 (1H, m); 1.55-1.67 (2H, m); 2.60 (1H, s); 2.76 (1H, s); 3.43 (3H, s); 4.47 (1H,s)	24.8; 28.2; 40.7; 43.8; 47.1; 56.0; 96,9; 167.2
6b	1-methoxy-2-methylpropene	70	1.45 (3H, s); 1.50 (3H, s); 3.41 (3H, s); 5.63 (1H,s)	14.5; 19.1; 58.7; 109.8; 141.3
7b	1-butoxy-2-methylpropene	130-135	0.85 (3H, t: 6.8); 1.2-1.6 (4H, m); 3.58 (2H;,t= 7.3); 5.72 (1H,t: ^4J= 2.5)	13.7; 14.8; 19.0; 19.4; 31.7; 71.4; 110.7; 140.0
8b	(*Z*^{c})-1-methoxy-2-thiomethoxy-3,3-dimethyl-1-butene	74-76 (15)	1.01 (9H, s); 2.06 (3H, s); 3.59 (3H, s); 6.17 (1H, s)	17.8; 28.9; 35.7; 59.7; 122.6; 147.2
9*E*b	(*E*^{e})-1-methoxy-2-ethylhexene^d	70 (28); 1.4315	0.85-0.99 (6H, m); 1.22-1.38 (4H, m); 1.67 (2H, t: ^3J= 5.0); 2.05 (2H, q: ^3J= 7.6); 3.51 (3H, s); 5.70 (1H, m: ^4J(ethyl-CH_2) =1.2 (t))	12.6; 13.9; 19.9; 22.4; 30.4; 30.8; 59.1; 120.2; 141.4
9*Z*b	(*Z*^{e})-1-methoxy-2-ethylhexene^d	68 (28); 1.4313	0.85-0.99 (6H, m); 1.22-1.38 (4H, m); 1.88 (2H, q: ^3J= 7.4); 2.04 (2H, dt); 3.49 (3H, s); 5.72 (1H, m: ^4J(butyl-CH_2) =1.3 (t))	13.1; 14.0; 22.7; 24.5; 26.5; 30.0; 59.1; 120.4; 141.3
10b	(*E*^{f})-1-methoxy-2-fenylbutene^d	60 (0.5)	1.00 (3H, t: ^3J= 7.5); 2.53 (2H, q: ^3J= 7.5); 3.62 (3H, s); 6.23 (1H, t: ^4J =0.6); 7.12-7.26 (5H, m)	13.1; 20.1; 59.8; 121.4; 125.7; 125.9; 126.2; 128.1; 128.3; 139.5; 144.7
13b	(*E*^{c})-1-methoxy-1-phenyl-3,3-dimethyl-1-butene	52 (0.5)	0.95 (9H, s); 3.57 (3H, 2); 4.84 (1H, s); 7.31-7.35 (5H, m)	32.2; 53.2; 54.9; 111.9; 127.7; 128.0; 129.8; 137.8; 154.3

(table 2 continued)

15b	1,1-dichloro-2,2,2-trimethoxyethane[d]		3.43 (9H, s); 5.75 (1H, s).	51.5; 72.0; 111.3.

a: configuration suggested because of the correspondance with the proton spectrum of vinylic chloride (ref. 32) b: configuration described in literature (ref. 30) corresponds with expected chemical shifts of protons adjacent to double bond ($R-CH_2-C=$). Part of ^{1}H-NMR data obtained from irradiation experiment (on 1.3 ppm). c: configuration based upon retention of configuration examined. (9E/Z, 10E) d: Spectra recorded on a Bruker AC300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz) e: Part of the spectrum information obtained by irradiation experiment (1.3 ppm); configuration based upon chemical shifts of protons adjacent to double bond.($R-CH_2-C=$); cis long range coupling constants were illucidated by irradiation of the adjacent proton of the ethyl and butyl group. trans couplings less than 0.5 Hz. f: configuration suggested on basis of long range coupling constant. (compare 9E/Z)

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