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MECHANISTIC ASPECTS OF REDUCTIONS OF ALLYLIC ETHERS AND ACETATES WITH ORGANOCUPRATES

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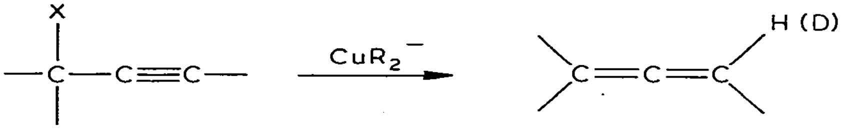
Summary

The rate of substitution to reduction has been investigated for reactions of three phenyl-substituted allylic ethers and the corresponding acetates with EtMgBr plus 10 or 25% copper(I) bromide in THF. It is found that the relative amount of reduction increases with increased electron delocalization in the postulated copper(III)-bound allyl ligand, and is also dependent on the nature of the leaving group; methoxy giving much more reduction product than acetoxy. Furthermore, for one acetate investigated there was more reduction at —65° C than at —25° C. The results are interpreted in terms of relative binding strength of allyl ligands to a copper(III) intermediate.

A number of reductions of acetylenic derivatives with organocuprates have been described. Thus, propargylic acetates [1,2,3], tosylates [4], chlorides [5], oxiranes [6] and methyl ethers [7,8] have been found to yield allenes in which hydrogen has been introduced in place of an alkyl group (eq. 1). In a few cases it has been shown that the hydrogen comes from water in hydrolysis of an organometallic intermediate [2,4,5,8]. Reductions of acetylenic hydrocarbons with organocuprates from Grignard reagents plus copper(I) iodide have been ascribed to copper(I) hydride formed by decomposition of the organocuprate [9].



(1)

Interestingly, no similar reduction of an allylic derivative with an organocuprate seems to have been described. In contrast cleavage of allylic ethers with Grignard reagents occur readily in the presence of cobalt(II) chloride [10], a reaction referred to as a radical reaction but which may have a more complicated mechanism [11].

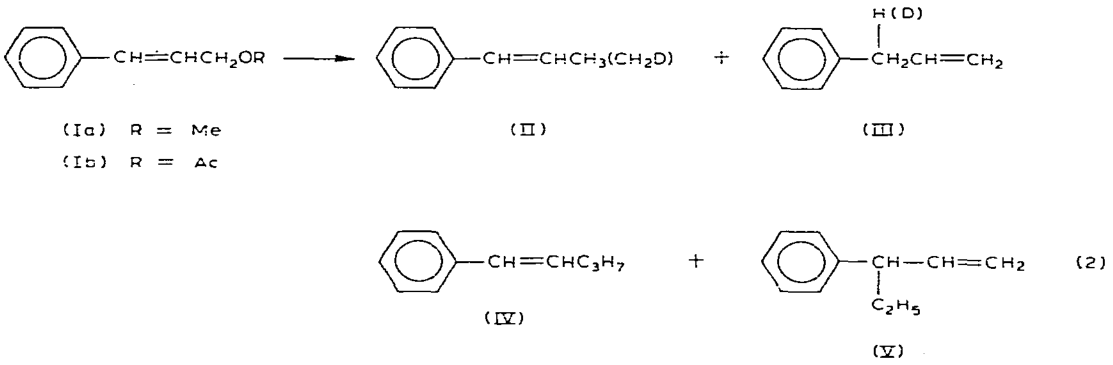
In order to increase the understanding of factors which influence the competition between substitution and reduction in reactions of organocuprates with unsaturated substrates we tried to bring about such reductions with allylic methyl ethers, and have found that it is possible to achieve almost complete reduction of allylic ethers provided they have a phenyl group attached in a way that allow mesomeric interaction in a postulated copper(III) intermediate (ethers Ia and VIa). The reagent used is a combination of ethylmagnesium bromide and 10 or 25% copper(I) bromide (or iodide) in THF as the critical solvent.

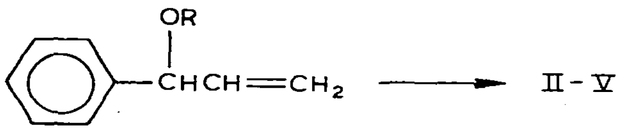
We also report here that the type of leaving group can determine the course of the reaction, since allylic acetates under the same conditions give rise to only trace amounts of reduction products. In addition, the solvent and the reaction temperature are other factors which influence the competition between reduction and substitution. Parts of the present findings have been published in a preliminary form [12].

Results

Initial experiments with the ether VIIa revealed that its reaction with EtMgBr plus 10% copper(I) bromide does not give rise to a reduction product in diethyl ether and only in THF is such a product formed. The experiments were therefore performed in this solvent according to the following standardised procedure (cf. Experimental). The allyl ethers Ia, VIa and VIIa were added to a five-fold excess of preformed cuprate (5 equiv. EtMgBr + 0.5 equiv. copper(I) bromide kept at —25° C). For the corresponding acetates 1.25 equiv. CuBr were used in order to get acceptable yields of substitution-reduction products instead of cleavage of the ester function. Removed samples were hydrolysed and analysed by GLC.

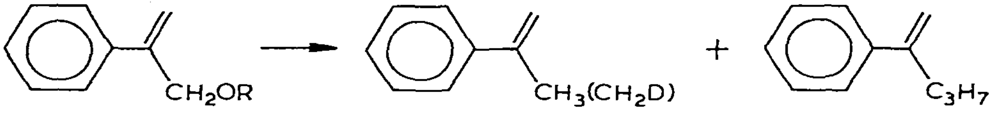
Under these conditions the ethers Ia and VIIa (eq. 2 and 4), reacted completely within a few minutes. The ether VIa reacted much more slowly and was consumed to only 60% after 2 h at —25° C; the reaction was complete after 15 h. Products were isolated by preparative GLC and identified (NMR, IR). The ethers Ia and VIa gave identical product mixtures consisting of compounds





(3)

(VIa) R = Me
(VIb) R = Ac



(4)

(VIIa) R = Me
(VIIb) R = Ac

(VIII)

(IX)

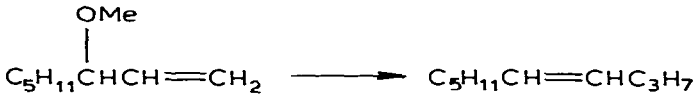
II—V plus minor unidentified components (<5%). The ratio between IV + V, the substitutions products, and the sum of II + III, the reduction products, was approximately 1/9 (Table 1). The relative amounts of compounds II and III varied from experiment to experiment and from sample to sample; compound II predominated over III in most cases. In all cases the ratio between the substitution products IV and V was >10. The ether VII (eq. 4) gave rise to the products VIII and IX in the relative amounts indicated in Table 1 (run 11). From the relatively slow reaction [13] of X (eq. 5) no reduction product, i.e.

TABLE 1

RELATIVE AMOUNTS OF REDUCTION (compounds II + III OR VIII) AND SUBSTITUTION (compounds IV + V OR IX) PRODUCTS IN THE REACTIONS OF ETHERS AND ACETATES (eq. 2—5)

Run	Compound	Temp. (°C)	Reduction (%)	Substitution (%)
1	Ia	—55	98	2
2	Ia	—25	90	10
3	Ia	0	93	7
4	Ia	—25	78[a]	22[a]
5	Ia	—25	87[b]	13[b]
6	Ia	—25	95[c]	5[c]
7	Ia	—25	94[d]	6[d]
8	Ia	—30	34[e]	66[e]
9	VIa	—25	90	10
10	VIa	—25	88[a]	12[a]
11	VIIa	—40	38[f]	62[f]
12	VIIa	—25	48[b]	52[b]
13	VIIa	—40	70[g]	30[g]
14	Ib	—25	13	87
15	VIb	—25	16	84
16	VIb	—65	61	39
17	VIIb	—25	6	94
18	X	0	<4	>96

[a] 25% CuBr was used. [b] Run with pure (99.99%) magnesium and CuBr · $(CH_3)_2S$. [c] 20% purified CuI and pure (99.99%) magnesium were used. [d] 20% non-purified CuI and magnesium purity (99.5%) were used. [e] Run in diethyl ether. [f] Mean of two runs. [g] 25% CuBr and 1% $CoCl_2$ were used.



$$C_5H_{11}\overset{\overset{\displaystyle OMe}{|}}{C}HCH{=}CH_2 \longrightarrow C_5H_{11}CH{=}CHC_3H_7 \qquad (5)$$

(X) (XI)

octene, could be detected (<4%); 4-decene in excellent yield was the only product (3-Ethyl-1-octene might have been formed in trace amounts but was not identified).

The acetates Ib, VIb and VIIb reacted with an excess of EtMgBr/CuBr (4/1) to give much less reduction product than the corresponding methyl ethers (runs 14, 15 and 17).

In two experiments with methyl ethers the amount of copper(I) bromide was increased to 25% relative to EtMgBr. This had no (run 10) or an almost negligible (run 4) effect on the reduction-substitution ratio.

In the standard procedure magnesium of ordinary Grignard quality (>99.5% Mg) and copper(I) bromide (ca. 99% CuBr) were used. To ascertain that the observed results were not caused by transition metal impurities we used magnesium (99.99% Mg) and purified $CuBr \cdot (CH_3)_2S$ or CuI [14] (runs 5, 6 and 12). There were no differences compared with the standard runs. On the other hand it was possible to increase the amount of reduction slightly by adding 1% (relative to EtMgBr) of cobalt(II) chloride to the cuprate before adding a methyl ether (run 13).

It was shown by deuterolysis of one reaction mixture that compound VIII is derived from an organometallic intermediate; 1.0 mol of deuterium was incorporated per mol of VIII (NMR). In the same way it was shown that compounds II and III are derived from the yellow intermediate which is formed instantaneously upon addition of Ia to the organocuprate.

In all of the above reductions it might be expected that the necessary corresponding oxidation product would be the dimer of the alkyl Grignard reagent. In order to facilitate quantitative determination of the yield of such a dimer we used pentylmagnesium bromide, which would give rise to decane. Thus in reactions of Ia in THF and in ether with this reagent combined with CuBr the following amounts of decane were formed; for Ia in THF 0.9 mol per mol reaction products (90% reduction) and in ether roughly 0.2 mol (20% reduction) i.e. amounts approximately equivalent to the amount of reduction.

The effect of varying the temperature was studied in runs 1—3 and 15—16. For the methyl ether Ia there were no significant differences in the interval —55—0°C whereas the reduction-substitution ratios for the acetate Vb were very different at —65 and —25°C (runs 15 and 16).

The influence of the solvent can be seen in runs 2 and 8; in diethyl ether (run 8) the amount of reduction is drastically reduced as compared with THF. In addition, the reaction rate in ether is much lower than in THF; the time for completion of run 8 is about 2 h while for run 2 it is a few minutes.

Discussion

Before proceeding to the discussion of the factors affecting the ratios of reduction and substitution we comment upon the unusual reactivity of the present reagent [13,7]. It is obvious that the reaction of allylic ethers such as VIa and X requires a powerful organocuprate reagent, since VIa is essentially unaffected by EtMgBr plus 0.5 equiv. of CuBr in THF at —25°C (unpublished results) and another allylic methyl ether was shown to be unaffected by lithium dimethylcuprate in ether [15]. We believe that the great reactivity of a reagent obtained in THF from a Grignard reagent and 5—10% of a copper(I) halide, preferably the bromide or chloride [13], can be explained by the presence of monomeric trialkylcuprate species. In analogy with e.g. the supernucleophile $Na_2Fe(CO)_4$ [16], which like organocuprates is a d^{10} complex, the doubly charged trialkylcuprates can also be expected to be highly nucleophilic. The assumption about their presence in the reaction mixtures we have used is based on the recent finding by Ashby and Watkins [17] that monomeric trimethylcuprate is formed when lithium dimethylcuprate is mixed with an additional equivalent of methyllithium in dimethyl ether or THF. As noted by Normant et al. [13] and by us [7], the choice of THF as the solvent is critical in increasing the reactivity of organocuprates derived from Grignard reagents (cf. Results). THF probably acts by complexing with magnesium ions and by bringing about dissociation of aggregates by coordinating to copper; both effects should increase the nucleophilicity of the organocuprate. Collman et al. [16] showed that ion-pairing decreases the reactivity of $Na_2Fe(CO)_4$. Pearson and Gregory have demonstrated the dimeric nature of lithium dimethylcuprate in diethyl ether, and used this to account for the tendency of the reagent to go through oxidative addition-reductive elimination cycles [18]. These authors thus invoke a mixed valence state for the two copper atoms which become part of the intermediate resulting from oxidative addition to an alkyl halide. On the basis of our reasoning above we disagree with this view of aggregate formation as an explanation of facile oxidative addition since, as mentioned above, we [7] and others [13] have shown increased reactivity of organocuprates under conditions where the presence of monomeric, highly nucleophilic trialkyl cuprate species may be expected. Ashby [24] has noted increased reactivity of $Li_2Cu(CH_3)_3$ in THF.

Factors affecting reduction-substitution

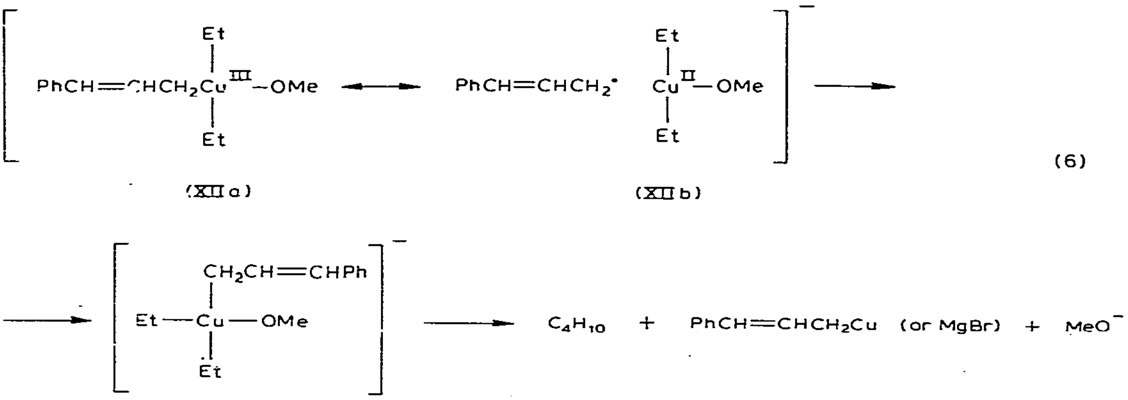
The present results reveal that four factors influence the ratio of reduction and substitution in the reactions of derivatives of allylic alcohols with an organocuprate (in our procedure obtained from EtMgBr and 10 or 25% CuBr). These are (i) the structure of the allylic compound, (ii) the nature of the leaving group, (iii) the temperature and (iv) the nature of the solvent.

The structure of an allylic methyl ether influences both the rate of reaction and the reduction-substitution ratio. The conjugation of the double bond with a benzene ring lowers the activation energy considerably, as evidenced by the differences between the rates of reaction of Ia and VIIa on the one hand and VIa and X on the other.

The identical reduction-substitution ratios obtained with Ia and VIa, and Ib and VIb point unambiguously to the fact that the same transient intermediate is formed after expulsion of the leaving group. It is now generally agreed that organocuprates give rise to a copper(III) or similar intermediate from oxidative addition [18]. In the case of Ia and VIa this intermediate may be depicted as

XII with two limiting structures. We have deliberately included methoxy as a ligand in this complex since we feel that this may be part of the explanation why methoxy, but not acetoxy, gives rise to reduction products (vide infra). The representation of XII with a σ-bonded allyl group is surmised from a comparison with π-allylnickel(II) complexes, which are known to become σ-complexed in the presence of good electron donors such as triphenylphosphine [19]. The different copper(III)-bond allyl ligands derived from Ia, VIIa and X may be loosely described as follows. The allyl ligand derived from Ia or VIa is a highly delocalized species and it is conceivable that it therefore is only loosely bound to the copper. The copper-bound allyl ligand derived from VIIa is only in part in mesomeric interaction with the benzene ring while the allyl group from X has no further π-orbital delocalization at all. The last mentioned group could in fact exist as a rather tightly bound σ- or π-allyl complex.

The different degrees of delocalization in the allyl ligands, whether as anions or radicals, is, however, only part of the story, and is in itself not an explanation of the different behaviour of the ethers. After its removal as methoxide the methoxy group must play a significant role in the postulated copper(III) intermediate. This role cannot be played by an acetate anion since the allylic methyl ethers and acetates differ markedly in the reduction-substitution ratio (Table 1). A very interesting hypothesis on the stabilization of copper(III) complexes has been forwarded by Pearson and Gregory [18] to the effect that while copper(I) is stabilised by soft ligands, which is obviously true, copper(III) might be stabilised by hard ligands. Since an alkoxide is a typical hard ligand there might be an extra stabilization of the intermediate obtained by oxidative addition when organocuprates react with unsaturated ethers; this is not attained by the acetates since the acetate ion should probably not provide any stabilization by binding to the copper. It might be relevant that the uniquely most stable methylgold(III) species is tetramethylaurate(III) [20,21]. We therefore suggest that an assumed loose binding of a highly delocalized allyl species to a copper(III) intermediate, when the copper at the same time binds a methoxide, will lead to rearrangements within the square copper(III) complex; this results in reductive elimination of the two alkyl groups and formation of a yellow allylcopper(I) or allylmagnesium bromide intermediate (eq. 6) which then gives rise to the observed reduction products upon hydrolysis (or deuterolysis). The copper(III)-bound allyl species may be pictured as an allylic anion (cf. the



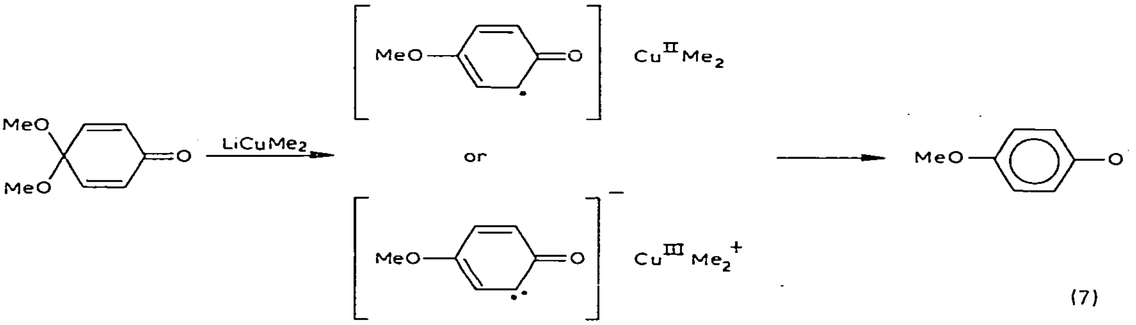
$$\left[\mathrm{PhCH{=}CHCH_2}\overset{\mathrm{Et}}{\underset{\mathrm{Et}}{\mathrm{Cu^{III}}}}\mathrm{{-}OMe} \longleftrightarrow \mathrm{PhCH{=}CHCH_2^{\bullet}}\ \overset{\mathrm{Et}}{\underset{\mathrm{Et}}{\mathrm{Cu^{II}}}}\mathrm{{-}OMe}\right]^{-} \longrightarrow \qquad (6)$$

(XIIa) (XIIb)

$$\longrightarrow \left[\mathrm{Et{-}}\overset{\mathrm{CH_2CH{=}CHPh}}{\underset{\mathrm{Et}}{\mathrm{Cu}}}\mathrm{{-}OMe}\right]^{-} \longrightarrow \mathrm{C_4H_{10}} + \mathrm{PhCH{=}CHCH_2Cu}\ (\text{or MgBr}) + \mathrm{MeO^-}$$

phenolate anion below). The process can also be thought of as occurring within an aggregate, with the allyl moiety (perceived as a radical, cf. XIIb) being reduced by another copper(II) complex. The latter process would leave two highly unstable Et_2Cu^{II} entities, which would immediately decompose to butane and copper(0) (cf. ref. 21). We have not noticed formation of colloidal copper as a result of the mixing of the reactants, but rapid disproportionation to copper(I) and copper(III) within an aggregate might explain this and would also lead to the actually observed roughly equimolar amounts of reduction product and alkane (decane from dipentyl cuprate).

The reaction depicted in eq. 7 provides further illustration of the soundness of the above reasoning [22]. In this case, however, it is difficult to assess the role of the expelled methoxide. We prefer to think of this reaction as proceeding via a copper(III)-bound phenolate anion.



(7)

However, the temperature affects the reduction-substitution ratio (runs 15 and 16) in the same direction as does the presence of the methoxy group. The same type of explanation can thus be invoked, i.e. stabilization of the copper(III) intermediate so that facile rearrangements within the complex can occur before the reductive elimination or, alternatively, reduction of the delocalized phenylallyl ligand by another cuprate. The difference between the reduction-substitution ratios in THF and ether (runs 2 and 8) might be explained in terms of a more compact copper(III) complex in the less dissolvating solvent diethyl ether, which is less likely than THF to coordinate to the copper. Thereby the allyl and alkyl ligands can bind tighter and rearrangements within the complex become less likely.

The present findings are in good agreement with our unpublished and partly published [8] observations regarding propargylic systems (eq. 1). The bearing of the results discussed above on the reduction of propargylic derivatives with organocuprates will be considered elsewhere.

Experimental

General

The starting ethers and acetates were prepared from the corresponding alcohols using standard procedures, or in the case of the acetate VIIb by oxidation of α-methylstyrene [23]. Their purity was checked by GLC. Reactions were monitored by GLC examination (Carbowax 20M columns) of hydrolysed samples. GLC runs were performed under conditions which would have allowed detection of dimers of the phenylallyl species. Products were isolated by GLC on 3 or 6 m long Carbowax 20M preparative columns. They were identified by NMR, IR and, in most cases, by mass spectrometry. Magnesium chips (purity > 99.99%) were obtained from Alfa Products (No. 00437). Copper(I) iodide (Merck) was purified three times by dissolving in saturated KI solution and then reprecipitated by diluting [14]. Copper(I) bromide (Riedel—de Haën) was used to form the dimethyl sulphide complex, which was recrystallised once [14].

General procedure for the reactions of ethers and acetates with organocuprates

To a solution of 40 mmol of ethylmagnesium bromide (from 99.5% Mg) in 25 ml of tetrahydrofuran, kept at —50° C under argon or nitrogen, 4 mmol (for ethers) or 9 mmol (for acetates) of copper(I) bromide (CuI in runs 6 and 7) was added in several portions. Alternatively, the Grignard reagent was added to a stirred suspension of CuBr in THF, and that caused no change in the product composition (checked on compound Ia), although the latter method always gave no visible decomposition of the organocuprate which sometimes occurred in the first procedure (bluish-black mixtures). The mixture was stirred for 15 min as the temperature was allowed to reach —25° C. An allyl ether or acetate (8—10 mmol), in THF was added by syringe at this or another temperature (Table 1) which was maintained throughout the reaction. The mixtures were hydrolysed by addition of water and worked up by standard procedures.

Reaction in the presence of cobalt(II) chloride

To the preformed cuprate (from 50 mmol EtMg and 12 mmol CuBr) kept at —50° C was added 0.6 mmol $CoCl_2 \cdot 6H_2O$; the mixture immediately started to turn black. 10 mmol of 2-phenyl-2-propenyl methyl ether (VIIa) was added after 5 min and the stirred reaction mixture was kept at —40° C. The starting material had disappeared after 20 min.

Reactions under iron-free conditions

The glassware used was thoroughly washed, rinsed with glass redistilled water, and dried in the oven. The magnetic stirring rod was encapsulated in glass. To prepare the organocuprate the Grignard reagent (from pure Mg, cf. above) in THF was added to a suspension of purified CuI or $CuBr \cdot (CH_3)_2S$ in THF kept at —60° C. The other reaction conditions were as described above.

NMR data for deuterated compounds II, III and VIII

IId: δ ($CDCl_3$) 7.5—7.0 (m, 5M), 6.6—5.9 (m, 2H), 2.0—1.7 (m, 2H) ppm.

IIId: δ ($CDCl_3$) 7.5—7.15 (m, 5H), 6.4—5.8 (m, 1H), 5.3—4.9 (m, 2H), 3.5—3.2 (m, 1H) ppm.

VIIId: δ ($CDCl_3$) 7.6—7.2 (m, 5H), 5.4 and 5.1 (two narrow m, 2H), 2.1 (narrow m, 2H) ppm.

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