Solvation Effects in the *Grignard* Reaction with Carbonyl Compounds

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Ratios of the yields of addition and reduction products for the reactions of butylmagnesium chloride with diisopropyl ketone, methyl 2-methylpropanoate, and isopropyl 2-methylpropanoate in toluene were determined at different THF, diethyl ether, and *tert*-butyl methyl ether contents in the *Grignard* reagent. Replacement of the alkoxy group in the ester leads to strikingly different results for very small additions of donors. The results are discussed in terms of the solvation of the species in the reaction mixture.

Introduction. – The most important reactions of *Grignard* reagents are those with carbonyl compounds. Formation of a tertiary or secondary alcohol is frequently accompanied by the reduction and enolization reactions lowering the yield of the target compound. It has been reported that reactions of ketones with alkylmagnesium bromides solvated with 1 equiv. of Et_2O or THF in benzene or toluene solution afford higher yields of addition products in comparison with those obtained in ethers as solvents [1].

Above all, the replacement of readily flammable ethers by solvents of high boiling point is important for large-scale organomagnesium syntheses. However, the use of hydrocarbon solvents offers additional advantages, since they are cheap and non-hygroscopic. In the presence of complexing agents, *e.g.*, ethers and tertiary amines, a great variety of organomagnesium compounds can be obtained in hydrocarbon media [2–7]. Primary, secondary, and tertiary alkylmagnesium chlorides in toluene solutions, which contain less than 1 equiv. of organic base, have been prepared recently [5–7].

Whereas the *Grignard* reagents in donor solvents are solvated by at least two solvent molecules per Mg-atom, those obtained in the presence of smaller molar amounts of donors are stoichiometrically only 'partially' solvated. Toluene proved to be a particularly suitable solvent for partially solvated *Grignard* reagents. While their solubility in alkanes is extremely low, one can obtain rather concentrated (1M and higher) solutions in toluene [4][6][7].

Although partially solvated *Grignard* reagents have also been used in large-scale industrial processes [5][8], their properties have been little investigated. One can expect several features different from those of conventional *Grignard* reagents.

Recently, we determined the ratios of the yields of reduction and addition products for the reaction of BuMgBr and BuMgCl with diisopropyl ketone ((i-Pr)$_2$CO) in various toluene/ether mixtures, scanning the donor content in the *Grignard* reagent from almost zero addition up to the partially solvated reagents [9][10]. The observed dependencies appeared to be complicated, including extreme points, the ratio addition/reduction (Add/Red) for conventional *Grignard* reagents being lower than that for

partially solvated reagents. The results were discussed in terms of the solvation of the reagents [10]. It became evident that partially solvated *Grignard* reagents can serve as tools for the investigation of the solvent effects in *Grignard* reactions.

In this work, the investigation was extended to alkyl esters. The main purpose of the work was a wider examination of solvation effects of donors to get insight into the mechanism of the control over formation of *Grignard* products governed by the solvation of the reactive species in *Grignard* solutions. Revised and complemented data for the reaction of (i-Pr)$_2$CO from our previous work [10] are also included and discussed more conclusively in this report.

Results. – We determined the yields of products from the reaction of BuMgCl in toluene with (i-Pr)$_2$CO, methyl 2-methylpropanoate and isopropyl 2-methylpropanoate in the presence of Et$_2$O, THF, or *t*-BuOMe.

The *Grignard* reagent, BuMgCl, was prepared in toluene with a catalytic amount of the ether (*ca.* 0.01 mole per mole of the halide). By addition of appropriate amounts of ethers to the obtained suspensions, *Grignard* reagents with different molar ratios of ethers were prepared. Previously, it was found [9][10] that the distribution of ether additions between the components of heterogeneous *Grignard* solutions arrived at completion within hours. Obviously, the fairly good solubility of the partially solvated *Grignard* reagents in toluene [6][7] favors the relatively rapid achievement of solvation equilibrium. In this way, the *Grignard* reagents containing very small amounts of ethers were obtained that could not have been achieved by direct synthesis [6][7].

Grignard reagents with different molar ratios of ethers were further allowed to react with the ketone in a molar ratio 1:2 (ketone to *Grignard* reagent), or with an ester in the molar ratio 1:3. The reaction products were quantitatively determined by means of GLC. The enolization process recovering the ketone or yielding a ketone (in the case of esters) was a minor side reaction, not exceeding 1–3%, except for a few points for methyl 2-methylpropanoate with the yields close to 6%. No ketolization was observed. Cautious quenching of the reaction mixture enabled us to prevent dehydration of the addition products.

The use of internal standards in GLC analysis allowed calculation of the material balance of the reaction. The sum of yields of addition and reduction products and of ketone (the enolization product) was always within the range of 97–102%.

Results of the experiments are presented in *Figs. 1–3*. The addition product of (i-Pr)$_2$CO is 2-methyl-3-isopropylheptan-3-ol and the corresponding reduction product is 2,4-dimethylpentan-3-ol (*Scheme 1*). For the esters, the recovered ketone is 2-methylheptan-3-one, and the addition and reduction products are 5-isopropylnonan-5-ol and 2-methylheptan-3-ol, respectively (*Scheme 2*).

All experiments, including the synthesis of BuMgCl, were repeated at least two to three times. In *Figs. 1–3*, the points indicate the mean values obtained from several experiments. The results of parallel experiments agreed within ± 5%.

As will be discussed below, the nucleophilic solvation of the Mg-atom favors both the addition and enolization, being less effective for the reduction reaction. Therefore, we use the molar ratios of the sum of addition and enolization products to the reduction product from the GLC analysis as reactivity characteristics for the *Grignard* reagents with different molar contents of the ethers.
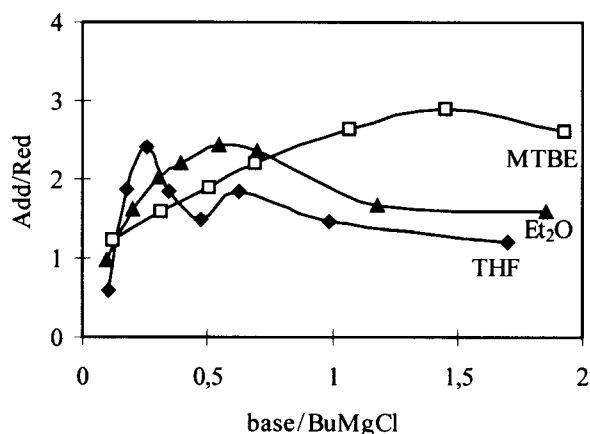
Fig. 1. *The ratios of yields of addition and reduction products* (Add/Red) *of (i-Pr)₂CO* vs. *the molar ratio of ether to* Grignard *reagent* (MTBE = t-BuOMe)
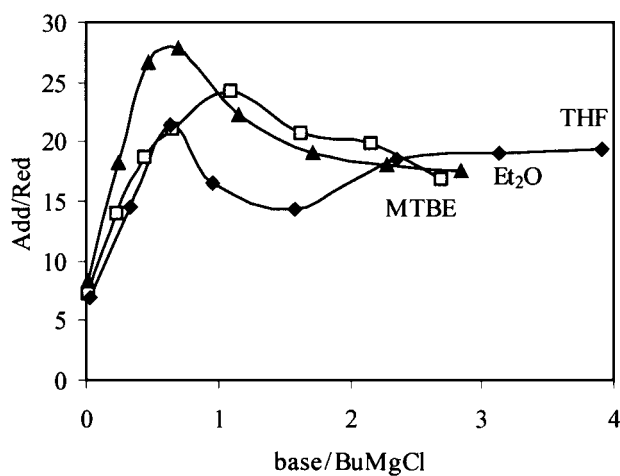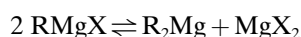

Fig. 2. *The ratios of yields of addition and reduction products* (Add/Red) *of isopropyl 2-methylpropanoate* vs. *the molar ratio of ether to* Grignard *reagent* (MTBE = t-BuOMe)

Discussion. – *Grignard*-reagent solutions usually contain an equilibrium mixture of variety of species. Apart from the association equilibria, the *Schlenk* equilibrium is essential:

$$2\,RMgX \rightleftharpoons R_2Mg + MgX_2$$

Both organomagnesium species are highly reactive toward ketones, but diorganyl-magnesium species react faster [11]. The primary reaction products, alkoxymagnesium species R′OMgX and RMgOR′, are able to complex other species in solution. Alkylmagnesium alkoxides are capable of alkyl addition to the carbonyl compound, but more by-products of enolization and reduction have been reported [12]. Alkylmagnesium alkoxides do not disproportionate with recovery of dialkylmagnesium
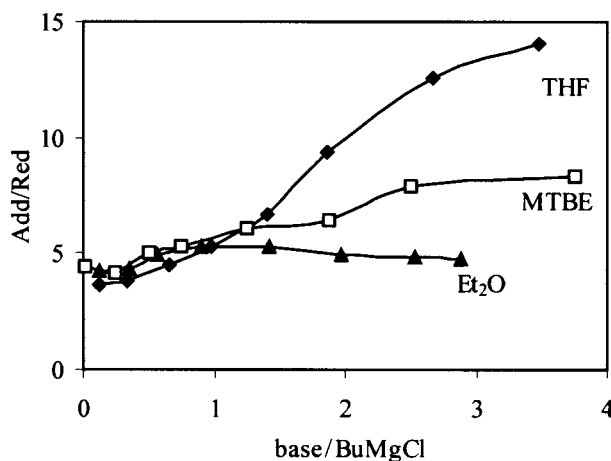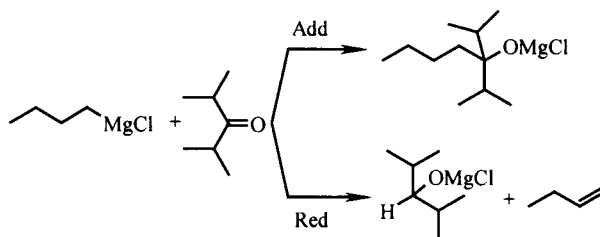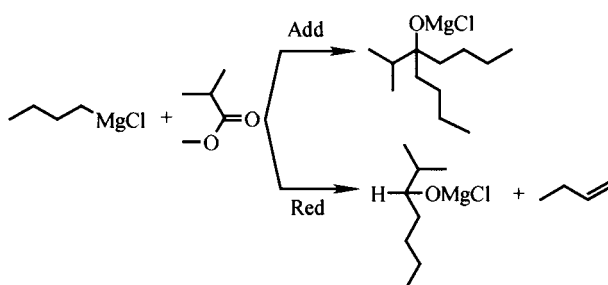
Fig. 3. *The ratios of yields of addition and reduction products* (Add/Red) *of methyl 2-methylpropanoate* vs. *the molar ratio of ether to* Grignard *reagent* (MTBE = *t*-BuOMe)

Scheme 1

Scheme 2

species in hydrocarbon solution, however, but $MgBr_2$ catalyzes the exchange reaction [13][14].

The general features of the *Grignard* reaction with ketones are well-understood now [15–17]. The coordination of the ketone with the Mg-atom is essential, and occurs by replacement of a donor molecule at the Mg-atom. Thus, one solvent molecule initially coordinated with the Mg-atom is present in the coordination complex, influencing its reactivity.

The heterolytic *Grignard* addition proceeds through a four-center transition state **I**, while a cyclic six-center transition state **II** is necessary for the reduction reaction [16].
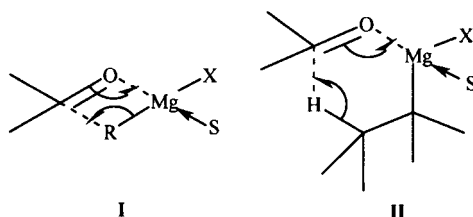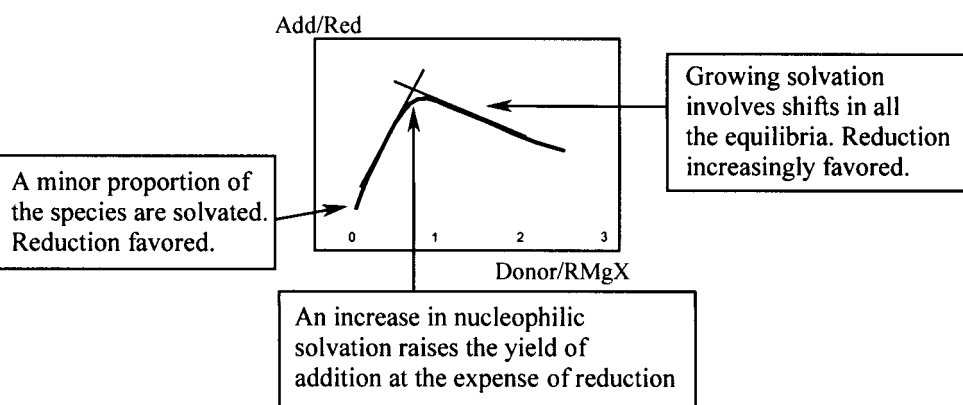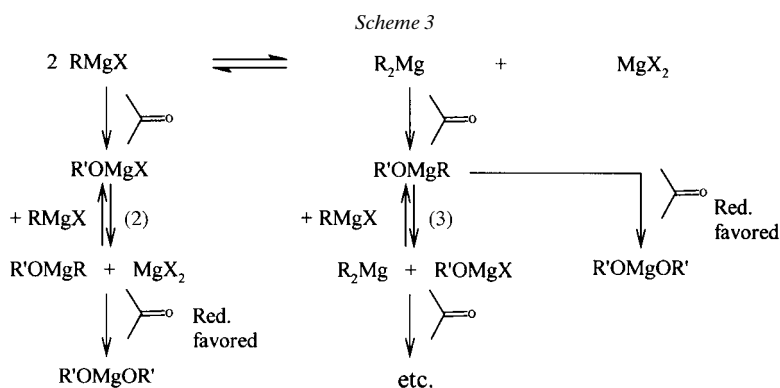

It is obvious that the nucleophilic solvation of the Mg-atom polarizes the $C-Mg$ bond, increasing the nucleophilicity of the C-atom and, thus, favoring the addition and enolization reactions. Reduction involves a β-H transfer, less influenced by the donor at the Mg-center. Consequently, an increase in the solvating ability of the donor should bring about an increase in the addition-reaction yield as well as in the extent of enolization. This conclusion is well-supported by the experimental data (*cf.* [18] and refs. cit. therein). An increase in the addition or enolization to the reduction ratio with an increasing effective basicity of the donors is evident.

It is also obvious that an increase in steric hindrance causes a decrease in solvating ability of the donor regardless of its *Brønsted* basicity. Likewise, the increasing bulkiness of the groups bound to the Mg-center hinders complexing between the donor and the substrate. One can conclude that very bulky alkoxy groups in magnesium alcoholates resulting from *Grignard* addition reactions considerably hinder complexation with donors, thus supressing the nucleophilicity of the organyl moiety. The consequence of this is the remarkable bias of R′OMgR species towards the reduction mentioned above. For this reason, the contribution of the reduction reaction increases during the process, particularly under preparative conditions, when a little or no excess of the *Grignard* reagent is used [19][20] (*cf. Scheme 3*).

Effectiveness of the solvation of the species is also important for the exchange reactions occurring in the reaction mixture. The primary products from the *Grignard* species RMgX and R_2Mg, and R′OMgX and R′OMgR, respectively, enter the dismutation equilibria *2* and *3* in *Scheme 3*. It is obvious that stronger solvation shifts equilibrium *2* towards the formation of MgX_2 species, similar to the *Schlenk* equilibrium [16][17], and equilibrium *3* towards RMgX formation. Thus, an increase in the solvating ability of the solvent increasingly produces R′OMgR species prone to reduce the carbonyl compound. It appears that a stronger solvation of the *Grignard* reagent in parallel to enhancement of the addition reaction can also favor the reduction reaction.

On the basis of the reasoning above, one can predict the course of the Add/Red ratio with increasing content of the donor in the *Grignard* reagent (*Scheme 4*).

The ratio Add/Red is minimal for small additions of the ethers. In this region, only a minor proportion of the species are solvated, thus largely favoring the reduction of ketone. An increase in nucleophilic solvation of the reagent raises the yield of the addition reaction at the expense of reduction, as discussed above. This part of the curve

Scheme 3

$$2\ RMgX \rightleftharpoons R_2Mg\ +\ MgX_2$$

R'OMgX   R'OMgR

+ RMgX (2)   + RMgX (3)

R'OMgR + MgX$_2$ R$_2$Mg + R'OMgX   R'OMgOR'

R'OMgOR'   Red. favored   etc.

Red. favored

Scheme 4

Add/Red

Growing solvation involves shifts in all the equilibria. Reduction increasingly favored.

A minor proportion of the species are solvated. Reduction favored.

Donor/RMgX

An increase in nucleophilic solvation raises the yield of addition at the expense of reduction

is expectedly steeper for more effective donors. However, growing solvation involves shifts in all equilibria, thus favoring, again, reduction of the ketone. As a result, the ratio Add/Red passes a maximum, expectedly located at greater additions of weaker donors. A further increase in the molar ratio of base to the *Grignard* reagent leads to the diminishing of the Add/Red ratio down to the value for the conventional reagent.

Our experimental results presented in the form of curves in *Fig. 1* are in good agreement with the predictions above.

The first points of the curves correspond to reagents partially solvated with the ketone at the beginning of the reaction and complexed with magnesium alcoholates by the completion of the reaction. Further donor additions are sufficient for solvation of only some portions of the strongest acid, MgCl$_2$, thus causing shifts of equilibria favorable for reduction. From a certain molar ratio of base to the *Grignard* reagent, effects fostering the addition reaction prevail and give rise to the curves discussed above.

Variation of the donor reveals a strong effect of solvation. The ethers employed in this work are of very similar *Brønsted* basicities; however, their effective basicities

differ largely, decreasing in the order THF > Et$_2$O > *t*-BuOMe, as it was shown also in our previous publication [7].

The addition reaction prevails over reduction, but the ratio Add/Red passes a maximum (or even two in the case of THF), exceeding the value for the reagent in pure ether (see [10]). *t*-BuOMe reveals a flat maximum only at greater amounts of the ether.

It was attractive to apply the conclusions drawn from reactions with ketone to those with esters. A characteristic feature of the reaction with esters consists in interim formation of a ketone and magnesium alcoholate. The ketone further reacts with another molecule of the *Grignard* reagent producing the addition or reduction products (*Scheme 5*). Magnesium alcoholates form stable complexes with *Grignard* reagents [15][16]. Obviously, the stabilities of the complexes strongly depend on the steric requirements of the alkoxy groups.
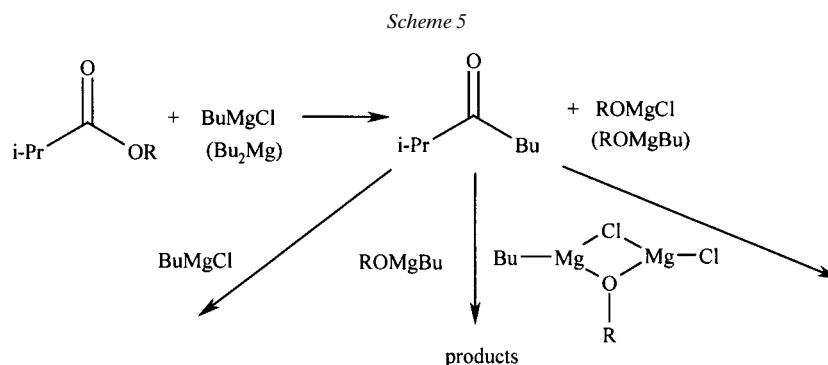
Scheme 5

As shown in *Scheme 5*, the reaction of the ketone can proceed *via* at least three pathways, *i*) with the ordinary *Grignard* reagent, *ii*) with the alkylalkoxymagnesium from the reaction with the ester, and *iii*) with the *Grignard*-alcoholate complex. The proportion of the alcoholate complexes gradually increases during the reaction. Thus, the determined Add/Red ratio is a critic value.

In *Figs. 2* and *3*, a significantly higher Add/Red ratio is seen for esters in comparison with the ketone. This is clearly due to the lower steric requirements of the intermediate ketone. Although the contribution of ROMgBu depends on relative reactivities of BuMgCl and Bu$_2$Mg towards the ester, its presence cannot be excluded, and it supposedly leads to an addition reaction of considerably greater extent than that with the species R'OMgBu (*cf. Scheme 3*).

The most impressive result of the experiment with esters is a dramatic diversity of patterns for the Add/Red ratio *vs.* molar ratio of ether to *Grignard* reagent. The only structural difference between the esters concerns the alkoxy moiety being either a MeO or an i-PrO group. The same moieties build up the alkoxymagnesium chlorides and their complexes with the initial *Grignard* reagent. Consequently, steric requirements of the alkoxy groups play a crucial role in the complexing equilibrium and in further reactions of the resulting complex.

For the isopropyl ester, the features of the plots Add/Red *vs.* molar ratios of the ethers (*Fig. 2*) are similar to those for diisopropyl ketone. This points to the interaction of the intermediate ketone with the *Grignard* reagent as a prevailing process in the

reaction mixture. The interpretation of the experimental data for diisopropyl ketone seems to be relevant also in this case. However, the maxima of the curves are shifted slightly to higher relative contents of Et$_2$O and THF, and to a smaller one of *t*-BuOMe. Most probably the levelling effect is related to a contribution of the reaction with the *Grignard*-alkoxymagnesium complex (see below).

On the contrary, plots for the methyl ester (*Fig. 3*) exhibit no distinct maxima. In addition, the ratio Add/Red is similar for all ethers and only slightly increases in the region up to the molar ratio of *ca.* 1.3. Greater ether contents differentiate the bases, THF being the most favorable for the addition reaction. This exceptional behavior of the methyl ester should be attributed to the strong donating ability of MeOMgCl. Obviously, the *Grignard* reagent is largely tied up to the alkoxide, and the reaction essentially proceeds with participation of the complex at lower molar ratios of an ether. Only greater additions of ethers can compete with the alkoxide, shifting the equilibria towards liberation of the *Grignard* reagent and, in this way, giving rise to a distribution of the products approaching but not identical to that for the isopropyl ester. Expectedly, THF as the most effective donor exerts the greatest influence on the equilibria.

The reason for the position of *t*-BuOMe relative to Et$_2$O is not clear, because, on the grounds of previous experimental data [7][10], *t*-BuOMe is reputedly a weaker base. Similarly, a bias of the alkoxide complex towards the reduction reaction is also a matter of speculation. As a possible explanation, different rigidities of the transition states of addition and reduction reactions should be considered (*Scheme 6*).

Scheme 6
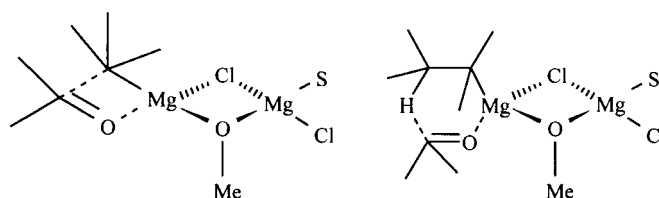
Simultaneous occurrence of two four-membered rings at a Mg-atom seems to be energetically less favorable than formation of a more-flexible six-membered transition state for the reduction reaction.

As an important conclusion, one can infer from the results for esters that their reactions, at least in the region of insufficient solvation, are strongly governed by the nature of the alkoxy group. Susceptibility of the process to steric effects is unexpectedly high. The key step of the reaction appears to be complexation between a *Grignard* reagent and the alkoxymagnesium compound. Replacement of Me group by slightly bulkier i-Pr group makes complexation unfavorable and switches the reaction to another pathway. It can also be concluded that sterically hindered alkoxy compounds resulting from reactions of ketones (*Scheme 3*) probably do not form stable complexes with the *Grignard* species in the presence of donor solvents.

Experimental Part

Commercial reagents were carefully purified. The reagents and solns. were operated on under dry Ar, and transferred by use of syringes. BuMgCl was prepared in toluene by using I_2-activated Mg turnings and BuCl in the presence of a small amount (*ca.* 0.01 mole of ether per mole of Mg) of Et_2O, THF, or *t*-BuOMe. The heterogeneous systems obtained usually contained *ca.* 1.5 mol of the *Grignard* reagent per l of toluene.

The basic Mg content in the reagent was determined by quenching an aliquot with the standard H_2SO_4. The excess acid was back-titrated against aq. NaOH. From the vigorously stirred mixture, 5-ml aliquots of the suspension were withdrawn and transferred to vials sealed with septa. Calculated amounts of the appropriate ether were added, and the reagents were left for a few hours or overnight. Then, (i-Pr)$_2$CO in the molar ratio 1:2 (ketone to *Grignard* reagent) or an ester in the molar ratio 1:3 dissolved in toluene was slowly added at $-15°$ to the reagents prepared as described above, and the mixtures were left overnight at r.t. The solns. also contained nonane or decane, i.e., the internal standard for GLC analyses.

Reaction mixtures were slowly quenched at $-15°$ by the dropwise addition of 10 ml of the 20% aq. soln. of NH_4Cl. The org. layer was separated and analyzed on a *Varian 3700* gas chromatograph with a cap. column *SGE BP 10* (0.3 mm × 24 m) and a flame-ionization detector. The reaction products were identified by their spectra. The ^{1}H- and ^{13}C-NMR spectra were acquired on a *Bruker AC-200 P* spectrometer in CDCl^3 with TMS as internal standard. The mass spectra were recorded on a GC/MS *Varian Star 3400* gas chromatograph with a cap. column *Alltech ECONO-CAP EC-5* (*SE-54*; 0.25 mm × 30 m) connected to an ion trap MS detector *Finnigan MAT Magnum*.

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