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DIVALENT LANTHANIDE DERIVATIVES IN ORGANIC SYNTHESIS—II

MECHANISM OF SmI_2 REACTIONS IN PRESENCE OF KETONES AND ORGANIC HALIDES[1,2]

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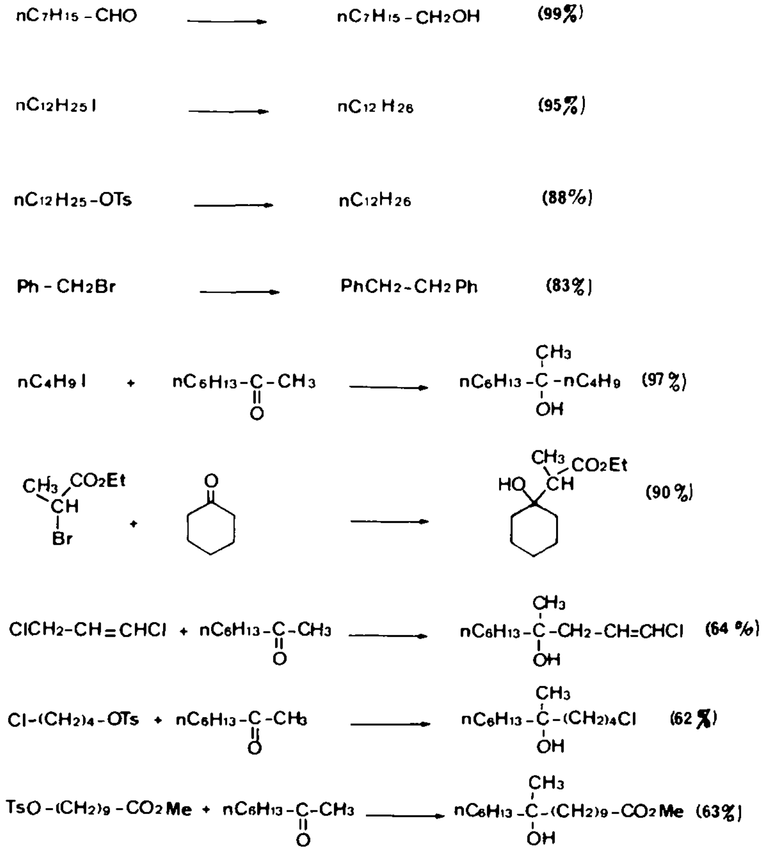
Abstract— Aprotic THF solutions of SmI_2 reduce alkyl halides or tosylates into the corresponding alkanes free of coupling products. The mechanism of this reaction involves an electron transfer from samarium to halides and hydrogen abstraction from THF. Aldehydes are selectively reduced by SmI_2 in presence of a proton donor. Ketones react with organic halides in the presence of SmI_2 giving tertiary alcohols. Mechanisms of these reactions are discussed. Some evidence including catalytic effects of $FeCl_3$ are given for electron transfers from SmI_2 towards ketones and halides.

INTRODUCTION

We recently established the usefulness of SmI_2 for mediating various organic reactions.[2] SmI_2 was easily prepared from samarium and 1,2-diiodoethane and can be stored as 10^{-1} M THF solution (THF = tetrahydrofuran). This reagent smoothly deoxygenates epoxides into olefins and sulphoxides into sulphides. SmI_2 selectively reduces aliphatic aldehyde into primary alcohol in the presence of aliphatic ketone. The reaction was performed in THF containing 2% of methanol. Aliphatic halides and tosylates were reduced into the corresponding alkanes in refluxing THF. No coupling products have been detected in this reaction. Quite the contrary dehalogenative dimerization occurs at room temperature with allylic or



Scheme 1. Some examples of SmI_2 reactions in presence of ketones and halides.[2]

benzylic halides. Grignard-type ketone addition of various organic halides are mediated by SmI_2. Tertiary alcohols are obtained after hydrolysis in high yields. Some representative examples of these reactions[2] are indicated in Scheme 1. In this paper we wish to discuss mechanisms of the reactions involving SmI_2 and ketones or/and organic halides.

DISCUSSION

Electron transfer processes from non-metal species towards organic compounds are still under wide investigation. Numerous works in the field of the organometallic reaction mechanisms have been described and several reviews are available.[3–8] In the reactions depicted in Scheme 1, SmI_2 behaves as an electron donor and appears as a new reagent able to promote various reactions which proceed by electron transfer. It is interesting to point out that SmI_2 presents a reduction potential[9] which is among the highest known for species soluble in organic medium:

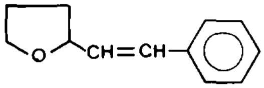
$$E_{0\,aq}Sm^{2+}/Sm^{3+} = -1.55\ V.$$

Reduction of organic halides

Two equivalents of SmI_2 convert alkyl bromides and alkyl iodides RX into the corresponding alkanes RH in refluxing THF. In these reactions we never observed the dimerization product R–R resulting from coupling of $R^\bullet$ radicals. In iodides reduction precipitation of SmI_3 occurs. Such a conversion performed by an electron donor is generally explained either by formation of a stable organometallic species which is transformed into alkane by subsequent hydrolysis or by a mechanism involving radical and/or anionic species, which are able to abstract hydrogen from THF.[10,11]

In SmI_2 reduction experiments no carbon-metal bond was detected by titrations of the resulting solutions after Sm^{2+} colour disappearance.[12] Furthermore these solutions are unable to alkylate ketones even though it was demonstrated that $RSmI_2$ or R_2SmI does (R = phenyl, methyl).[13] Hydrolysis by D_2O of the same resulting solutions leads to a non-deuterated alkane. Thus, a mechanism involving formation of a stable organometallic species may be dismissed.

In the reaction between β-bromostyrene and SmI_2, appreciable amounts[14] of "solvent adduct" hydrocarbon **1** were obtained (22%) besides the recovered β-bromostyrene (64%). Product **1** could arise from combination of the radicals $THF^\bullet$ and $C_6H_5–CH=CH^\bullet$.



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Thus, the mechanism involving radical species is the most likely for the reduction of organic halides by SmI_2 (Scheme 2).

$$RX + Sm^{2+} \longrightarrow RX^{-\bullet} + Sm^{3+}$$

$$RX^{-\bullet} \longrightarrow R^\bullet + X^-$$

$$R^\bullet + Sm^{2+} \longrightarrow R^- + Sm^{3+}$$

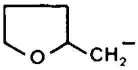
$$R^\bullet + SH \longrightarrow RH + S^\bullet$$

$$R^- + SH \longrightarrow RH + S^-$$

(SH solvent)

Scheme 2.

In some circumstances transient carbanionic species are probably present in the medium. For example, reaction between tetrahydrofurfuryl bromide and SmI_2 leads to large amounts (50%) of 4-penten-1-ol which result from the classical rearrangement[15] of the tetrahydrofurfuryl anion **2**.



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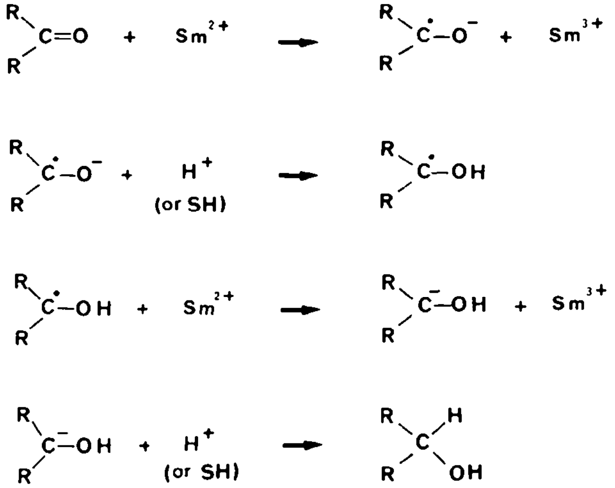
Contrary to alkyl halides, reduction of benzylic or allylic halides by one equivalent of SmI_2 lead primarily to dimerized products at room temperature. Radicals and carbanions arising from these halides are particularly stable. Moreover nucleophilic substitutions are quite easy on these substrates. In order to explain our results, we assumed that radicals, being stable enough, can diffuse outside the coordination sphere of samarium, leading to coupling products. Another hypothesis is that carbanions are sufficiently stable and abundant for further reaction with remaining halide.[16]

Alkyl tosylates are reduced into alkanes by two equivalents of SmI_2 in refluxing THF. These reactions are enhanced by small amounts of NaI. Thus, the first step is probably the conversion of tosylates into iodides,[17] followed by the reduction to alkanes. As a matter of fact, even in absence of NaI small amounts of alkyl iodides are detected among the reaction products.

Reduction of carbonyl group

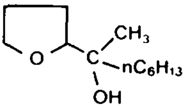
The reduction of ketones by metals dissolved in ammonia or alcohol and the related electrochemical reductions have been extensively studied. These works have been summarized.[18] The reduction of carbonyl groups by SmI_2 could be described by a scheme analogous to the classical one where SmI_2 behaves as an electron donor (Scheme 3).

The first step is the formation of a ketyl radical-anion. Two equivalents of SmI_2 per ketone and a proton donor are necessary. This mechanism is supported by the following observations. In 2-octanone reduction, in addition to the expected 2-octanol, small amounts of pinacolization products and of "solvent adduct" alcohol **3** are detected. This reveals



Scheme 3.

the existence of ketyl intermediates in the reaction medium.[19]

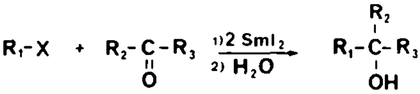


3

The reduction of octanal by SmI_2 performed in presence of CH_3OD leads mainly to the C-deuterated 1-octanol. A small amount (10%) of non-C-deuterated 1-octanol was also detected. Similar results have been obtained in the reduction of acetophenone in presence of D_2O. These experiments show that, concurrently to the proton donor methanol (or water), the solvent tetrahydrofuran has to be also considered as an hydrogen donor. Octanal was also partially reduced in aprotic SmI_2–THF solution. Subsequent hydrolysis by D_2O gave no C-deuterated 1-octanol. This reveals that a ketone dianion is not the end-product before hydrolysis in the reduction reaction. Thus the Scheme 3 is the most appropriate for the reduction of carbonyl groups by SmI_2.

Condensation between a ketone and an organic halide

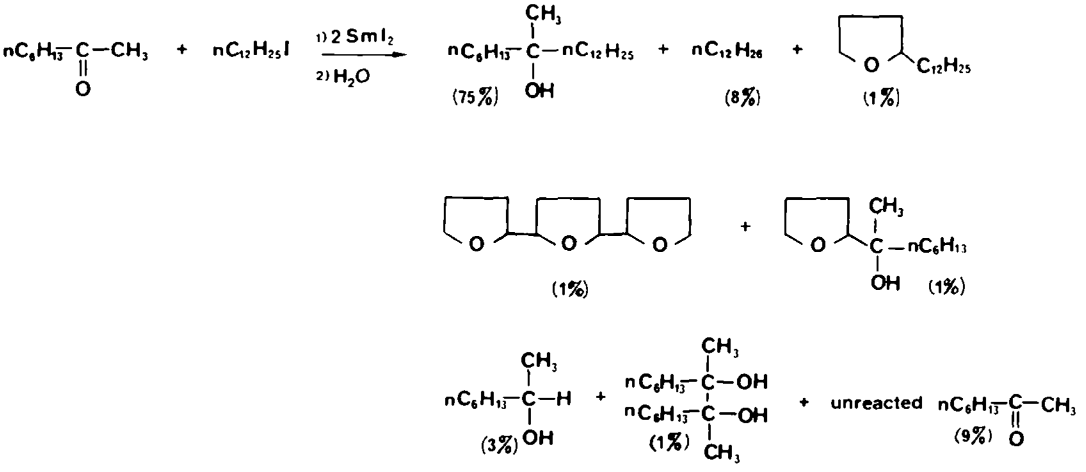
One of the most useful applications of SmI_2 was its ability to induce selective C–C bond formation between ketones and various organic derivatives RX (X = halide or tosylate).[2] Some examples of these reactions (eqn 1), which formally resemble to Grignard-type carbonyl addition, have been listed in Scheme 1.



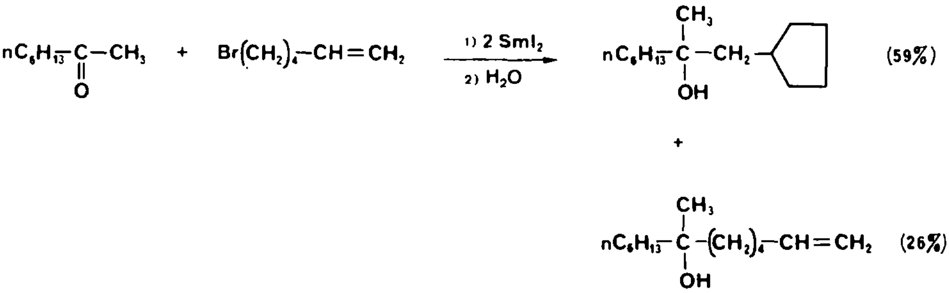
$$R_1\text{-}X + R_2\text{-}\underset{\overset{\|}{O}}{C}\text{-}R_3 \xrightarrow[2)\,H_2O]{1)\,2\,SmI_2} R_1\text{-}\underset{OH}{\overset{R_2}{C}}\text{-}R_3 \qquad (1)$$

In order to obtain mechanistic informations, a complete analysis of reaction products in the alkylation of 2-octanone by 1-iodododecane in presence of two equivalents of SmI_2 was carried out with the help of a coupled gc-mass spectrometer (Scheme 4).

7-methyl-7-nonadecanol and unreacted 2-octanone are obtained in 75% and 9% yield respectively. The most abundant by-product is dodecane. The presence of THF radicals in the reaction medium and/or THF$^-$ carbanions is revealed by formation of small amounts of various 2-substituted THF. Ketyl radicals also are



Scheme 4.



Scheme 5.

present: pinacolization products of 2-octanone, "solvent adduct" alcohol and 2-octanol are detected.[19] Thus the main by-product is the hydrocarbon which results from the reduction of alkyl halide by SmI_2. This explains why an excess of both SmI_2 and alkyl halide allows tertiary alcohol to be obtained almost quantitatively.[2]

In the alkylations mediated by SmI_2, $R^{\cdot}$ radicals and ketyl radicals are obviously present in the reaction medium. This is supported by examination of by-products arising in these reactions, as pointed out in Scheme 4. A classical test for detection of radicals is the use of 1-bromo-5-hexene, a precursor of a hexenyl radical which is able to cyclize into methylcyclopentyl radical.[20] Reaction between 2-octanone and 1-bromo-5-hexene performed in the presence of SmI_2 is described in the Scheme 5. Since cyclopentane ring formation is clearly observed, a radical species was involved during the course of the reaction.[20]

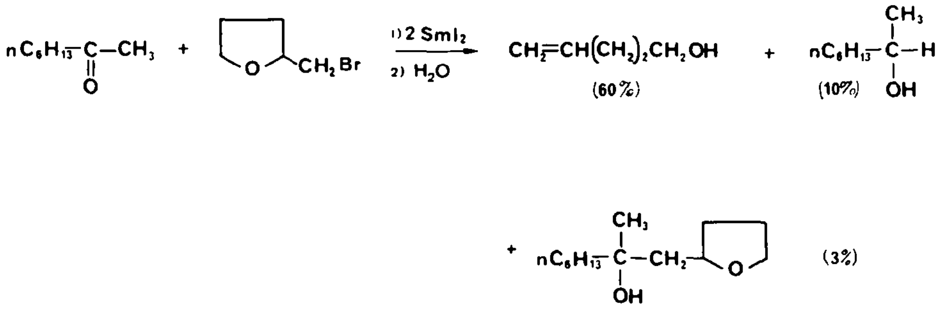
It is interesting to point out that in the absence of ketones and under conditions leading to hydrocarbons, 1-bromo-5-hexene does not lead to methylcyclopentane. In the same vein, benzylic or allylic halides react in the absence of ketones with SmI_2 to yield coupling products exclusively while only tertiary alcohols are obtained when 2-octanone is present as well; furthermore the dehalogenative dimerization is very rapid. For example benzylbromide leads to dibenzyl in 82% yield in 20 min. In the presence of 2-octanone alkylation is slower, giving as the only product the tertiary alcohol in 69% yield in 30 min. These experiments, showing that SmI_2 behaves in different ways towards allylic or benzylic halides depending on the presence of a ketone, suggest that this latter strongly complexes to SmI_2 and could be in addition a relay for electron transfer. In the reaction between SmI_2 and 1-bromo-5-hexene, in absence of ketones, we consider that $R^{\cdot}$ radicals are rapidly reduced by SmI_2 into carbanions R^-, this reaction being faster than $R^{\cdot}$ cyclization. Hexenyl anion cyclization can not occur.[15,20] Abstraction by R^- carbanion of a proton from THF molecule completes the reaction.

Optically active 2-bromooctane reacts with cyclohexanone at room temperature, in presence of SmI_2, to give a racemic tertiary alcohol. The same result is obtained using optically active ethyl 2-bromopropionate and cyclohexanone. Loss of optical activity is expected if alkyl halide was converted into a radical and/or a carbanion. These experiments exclude an alkylation mechanism involving a nucleophilic substitution of the alkyl halide by the ketone dianion **4**.

In some particular cases, alkyl anions intermediates can be formed in the reaction medium. Thus, tetrahydrofurfurylbromide reacts with SmI_2 and 2-octanone to give mainly 4-penten-1-ol, arising from rearranged tetrahydrofurfuryl anion[15] (Scheme 6).

Alkylation of ketones by alkyl tosylates was also carried out in presence of SmI_2. Such a reaction starts probably by the conversion of alkyl tosylate into alkyl iodide,[17] the alkylation of ketone occurring then through a mechanism like the one discussed above. As a proof, catalytic amounts of NaI enhance this alkylation reaction, and alkyl iodides even in absence of NaI are present in the reaction products.

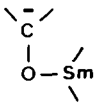
Addition of catalytic amount of ferric chloride (1% with respect to SmI_2) decreases the reaction time of the alkylation mediated by SmI_2.[2] This effect of $FeCl_3$ could be related to its ability to catalyze formation of ketyl radicals as described recently in Grignard-type



Scheme 6.

reactions[21] and/or conversion of Ln^{2+} into Ln^{3+} derivative.[22] These two effects could exist in the experiments mediated by SmI_2, where $FeCl_3$ appears as a species facilitating electron transfers.

Three mechanisms may be considered in order to rationalize experimental results: (i) the reaction occurs by successive electron transfers to alkyl halide RX producing a R^- carbanion, probably as a transient Grignard-like reagent $RSmI_2$ able to alkylate ketones; (ii) simultaneous electron transfers to alkyl halide RX and ketone give rise to a $R^{\cdot}$ radical and a ketyl radical and upon coupling and subsequent hydrolysis, these two species yield alkylation product; (iii) electron transfer to the ketone leads to an alcoholate anion such as **4** and alkylation of this species by alkyl halide RX through a nucleophilic substitution yields after hydrolysis the expected alcohol.



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More complex mechanistic schemes including intermediate species coordinated to metal may be considered. Scheme 7 takes into account all the mechanistic processes envisaged for the alkylation of ketones by organic halides in the presence of SmI_2. The above experiments show that a mechanism involving radical species is the most likely (mechanism ii). Nevertheless, according to each studied system, some of the steps indicated in the Scheme 7 may or not be involved in the mechanism of particular alkylation reaction.

As other lanthanide derivatives, SmI_2 presents a high coordination number, usually seven.[23] We believe that the alkylation reactions occur in the coordination sphere of samarium which is bonded to several molecules of THF.

In the Scheme 7 species required for these reactions are indicated between brackets, their exact stoichiometry and their solvation or association degrees being not exactly known.

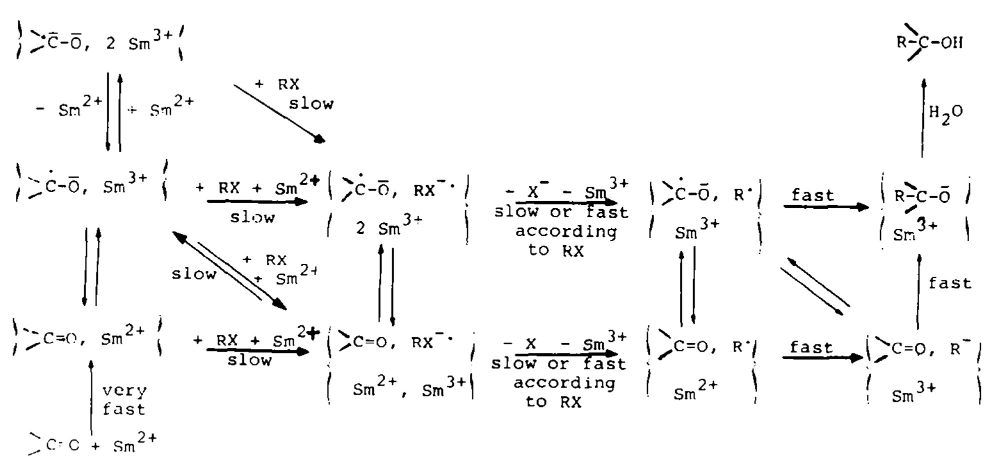
The formation of all the by-products of Scheme 4 can be explained by some of the pathways proposed in Scheme 7. THF radicals formed by hydrogen abstraction from THF by a radical species $R^{\cdot}$ (or a ketyl radical) can react with another radical $R^{\cdot}$ (or a ketyl radical) leading to the "solvent adduct hydrocarbon" or to the "solvent adduct alcohol". Abstraction of hydrogen from THF converts radical R or ketyl radical into "reduction hydrocarbon" RH or "reduction alcohol" respectively. The small amounts of "pinacolization products" arise from the dimerization of transient ketyl radicals.

Thus in the alkylation of a ketone by an alkyl halide performed in presence of SmI_2, a mechanism including radical species is the most probable, the expected tertiary alcohol resulting from the coupling of a radical $R^{\cdot}$ with a ketyl radical. However other pathways depicted in Scheme 7 must not be excluded for the mechanism of some particular alkylations and more detailed studies would be necessary to improve the mechanistic schemes of SmI_2-mediated reactions.

CONCLUSION

A picture of the mechanisms involved in SmI_2-mediated reactions is now emerging. The main characteristic of this soluble reagent is its ability to transfer one electron to organic halides RX with subsequent formation of radical species $R^{\cdot}$. Electron transfer towards ketones is also possible. Thus radical chemistry is initiated by SmI_2. However the presence of highly coordinated Sm^{2+} and Sm^{3+} derivatives is determinant. It probably facilitates electron transfer and could change some of the usual reactions of radical $R^{\cdot}$. For example no coupling product R–R could be obtained from an alkyl halide RX even in absence of ketone; in such a case hydrogen abstraction from THF is the only reaction.

More mechanistic studies are necessary to widely explain the reactivity of SmI_2 which appears as a new



Scheme 7. Some tentative pathways of ketone alkylation by an alkyl halide mediated by SmI_2.

reagent able to promote many selective transformations in organic molecules. Scope of the SmI_2 reactions in organic synthesis is under investigation.

EXPERIMENTAL SECTION

Proton magnetic resonance spectra (^1H NMR) were recorded on a Perkin-Elmer Model R 32 at 90 MHz. Chemical shifts in $CDCl_3$ are reported in ppm on the δ scale relative to tetramethylsilane as internal standard. Mass spectra were obtained on a GC-MS Hewlett-Packard Model 5992 A. Gas chromatographic analyses were carried out on a Carlo Erba Model FTV 2150. Peak area integration were performed by electronic integration. Yields measured by GLC were all calculated by comparison with an internal standard. Optical rotations were measured using a Perkin-Elmer Model 241 polarimeter.

Reagents and reaction procedure

THF solutions of samarium diiodide were prepared as described in reference 2. Samarium was 40 mesh powder from Labelcomat (Belgium). THF must be deoxygenated and quite anhydrous. 1,2-diiodoethane (Merck) was purified as in reference 2. Sodium iodide and ferric chloride are dehydrated before use. Most organic compounds used are commercial samples purified by distillation or recrystallization. Tetrahydrofurfurylbromide,[24] (−) 2-bromooctane,[25] (+) ethyl 2-bromopropionate[26] and sulfonates[27] were prepared according to literature procedures.

Unless otherwise stated, all operations, the reactions between SmI_2 and various substrates such as the analysis of reaction products, were carried out in the same way as previously described.[2] Many spectra of reaction products may be compared with those of authentic samples prepared by Grignard reactions or Reformatsky reactions. Reduction experiments leading to deuterated or non-deuterated products have been analyzed with the help of a coupled GC-mass spectrometer. This apparatus has been also used for the analysis of by-products in the alkylation reaction of 2-octanone by 1-iodododecane.

1-*Phenyl*-2:2′-*tetrahydrofuryl-ethylene* (**1**). ^1H NMR 1.60–2.20 (m, 4, $J = 7$ Hz, H heterocyclic), 3.92 (m, 2, $J = 7$ Hz, H heterocyclic), 4.48 (q, 1, $J = 6$ Hz, $J' = 7$ Hz, H heterocyclic), 6.20 (d.d., 1, $J = 16$ Hz, $J' = 6$ Hz, $C_6H_5\ CH{=}C\underline{H}$), 6.62 (d, 1, $J = 16$ Hz, $C_6H_5{-}C\underline{H}{=}CH{-}$) 7.30 (m, 5, Arom); Mass spectrum *m/e* 174 (100, M^+) 146 (10), 132 (13), 131 (55), 104 (51), 103 (27), 91 (20), 77 (25).

2:2′-*Tetrahydrofuryl-octan*-2-*ol* (**3**). Mass spectrum *m/e* 200 (3, M^+) 185 (4), 130 (8), 129 (100), 115 (39), 71 (29), 69 (69), 55 (14).

1-*Tetrahydrofuryl-dodecane*. (Scheme 4) mass spectrum *m/e* 240 (28, M^+), 197 (39), 169 (46), 71 (100), 59, 43.

2:2′, 5′.2″-*Tertetrahydrofuran*. (Scheme 4) mass spectrum *m/e* 213 (6, MH^+) 71 (6), 59 (100), 43 (11).

2-*Methyl*-1:2′-*tetrahydrofurfuryl-octan*-2-*ol*. (Scheme 4) mass spectrum *m/e* 129 (10), 126 (25), 113 (61), 85 (50), 71 (41), 58 (39), 55 (100), 43 (78).

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