

Journal of Organometallic Chemistry, 186 (1980) 173–184
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BIS(1,4-DIHYDRO-1-PYRIDYL)ZINC AND BIS(1,4-DIHYDRO-1-PYRIDYL)MAGNESIUM COMPLEXES; REDUCING PROPERTIES OF THE 1,4-DIHYDROPYRIDYL GROUP BOUND TO ZINC OR MAGNESIUM

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(Received August 20th, 1979)

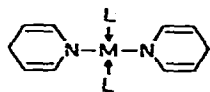
Summary

Bis(1,4-dihydro-1-pyridyl)zinc and -magnesium complexes are mild reducing agents. These compounds contain metal-bound 1,4-dihydropyridyl groups which act as hydride donors.

In this paper we report the reactions of these new reagents with compounds which contain a carbonyl group, viz. ketones, aldehydes, enones and carboxylic esters. The stereochemistry of the reduction of cyclic ketones by bis(1,4-dihydro-1-pyridyl)zinc and -magnesium complexes has been studied. In reactions with carboxylic esters no reduction was observed; instead, acylation of one of the 1,4-dihydropyridyl groups bound to the metal took place yielding (novel) *N*-acyl-1,4-dihydropyridines. The scope of the reductions by the bis(1,4-dihydro-1-pyridyl)metal complexes is outlined, and the possible biological implications of the study are discussed.

Introduction

In the preceding paper [1] the synthesis and characterization of novel 1,4-dihydro-1-pyridylzinc and -magnesium complexes were described. They are made from ZnH_2 or MgH_2 and pyridine. In the case of zinc the coordinated pyridine molecules could be easily replaced by the bidentate ligand *N,N,N',N'*-tetramethylethylenediamine (TMED).



M = Zn,	L = pyridine;	complex B*
M = Zn,	2L = TMED;	complex C
M = Mg,	L = pyridine;	complex D

* This notation is identical to that used in ref. 1.

One of the most striking properties of these complexes, which do not contain metal-hydrogen bonds, is their selective reducing ability. Ketones, aldehydes and imines are easily reduced. This paper deals with the scope and the stereoselectivity of these reductions and with the specific role of the metals in the action of the reducing agents.

Results

Reduction of ketones and aldehydes

The pyridine complexes of bis(1,4-dihydro-1-pyridyl)zinc, complex B, and bis(1,4-dihydro-1-pyridyl)magnesium, complex D, readily reduce ketones and aldehydes and after hydrolysis the corresponding alcohols are obtained. The TMED complex of bis(1,4-dihydro-1-pyridyl)zinc, complex C, also exhibits this reducing ability.

The reductions are carried out in THF at room temperature for 24 hours, with a 1 : 1 ratio of reducing agent to ketone. Benzophenone, acetophenone and methyl sec-butyl ketone, taken as examples of diaryl, aryl alkyl, and dialkyl ketones, respectively, are reduced by either of the complexes in yields greater than 80%. Under the same conditions benzaldehyde and decanal are reduced to benzyl alcohol and 1-decanol.

When an excess of a ketone or aldehyde is treated with either of the bis(1,4-dihydro-1-pyridyl)metal complexes the first equivalent of hydride from the 1,4-dihydropyridyl groups bound to zinc or magnesium is transferred more rapidly than the second. There is also a difference in reactivity towards ketones and aldehydes between the pyridine complex of bis(1,4-dihydro-1-pyridyl)zinc (B), its TMED analogue (C), and the pyridine complex of bis(1,4-dihydro-1-pyridyl)magnesium (D); complex B generally reacts faster than the complexes C and D.

The reduction of ketones and aldehydes can also be carried out in less polar organic solvents such as diethyl ether, benzene, or pentane, but the reactions are then much slower.

Stereoselectivity in the reduction of cyclohexanones





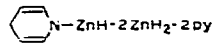
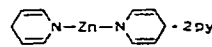
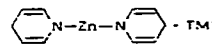
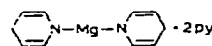
In order to study the stereoselectivity of the new reducing agents they were treated with 4-tert-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, 2-methylcyclohexanone and camphor. The results are summarized in Table 1.

The stereoselective reduction of cyclohexanones by metal hydrides has been studied extensively in recent years [2,3]. LiAlH_4 is considered to be the least sterically hindered hydride, since it produces 91, 76 and 22% axial attack on 4-tert-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, and 2-methylcyclohexanone, respectively [2]. The more bulky hydrides are subject to "steric approach control" [4] in their reactions with a given cyclohexanone and the amount of equatorial attack can be considered as indicating the effective bulk of the hydride.

4-tert-Butylcyclohexanone provides a good example of the chair form of cyclohexanone. The tert-butyl group is locked in an equatorial position and directed away from the reaction center. Its inductive, steric and field effects on the reaction center should thus be minimal, and so the data in Table 1 for this

TABLE 1

RELATIVE YIELDS ^a OF AXIAL, CIS OR EXO ALCOHOL IN THE REDUCTION OF SOME SUBSTITUTED CYCLOHEXANONES AND CAMPHOR BY LiAlH₄, ZnH₂, MgH₂ AND 1,4-DIHYDRO-1-PYRIDYL METAL COMPLEXES DERIVED FROM THE LAST TWO HYDRIDES (THF, ROOM TEMPERATURE, 24 HOURS)

Reducing agent ^b	 4-tert. Bu- cyclohexanone	 2-Me- cyclohexanone	 3,3,5-triMe- cyclohexanone	 camphor
LiAlH ₄	9 (100) ^c	24 (100)	78 (100)	91 (100)
ZnH ₂	35 (100)	52 (100)	85 (100)	92 (100)
MgH ₂	70 (8)	67 (15)	18 (5)	94 (18)
 (A)	27 (100)	43 (100)	88 (100)	94 (100)
 (B)	11 (90)	37 (100)	69 (89)	72 (100)
 (C)	13 (67)	39 (96)	75 (40)	90 (42)
 (D)	9 (66)	42 (96)	56 (65)	48 (35)

^a Normalized as % axial alcohol + % equatorial alcohol = 100%; the ratio is measured by GLC analysis.

^b The molar ratio reducing agent to ketone was 1 : 1. ^c The total yield of the reduction, as determined by GLC, is given in parentheses.

ketone should represent accurately the ratio of axial: equatorial attack on the chair form of cyclohexanone. Comparing LiAlH₄, MgH₂, ZnH₂ and the bis(1,4-dihydro-1-pyridyl)metal complexes in the reduction of 4-tert-butylcyclohexanone, the amount of axial alcohol increases in the order (C₅H₆N)₂Mg · 2 py (D) ≈ LiAlH₄ < (C₅H₆N)₂Zn · 2 py (B) < (C₅H₆N)₂Zn · TMED (C) < ZnH₂ << MgH₂. These results in THF suggest that the highest effective bulk is that of MgH₂ if it is assumed that the steric requirement of the reagent is the determining factor for the stereoselectivity of the reduction. The bis(1,4-dihydro-1-pyridyl)metal complexes demonstrate a steric hindrance in axial attack comparable to that of LiAlH₄. The experimental data correlate very well with the chemical properties of the reducing agents. MgH₂ and ZnH₂ are considered to be highly associated hydrogen-bridged coordination polymers, insoluble in THF. LiAlH₄ is primarily present in THF as a solvent-separated ion pair [5], and the bis(1,4-dihydro-1-pyridyl)metal complexes are probably monomeric four-coordinated species, moderately soluble in THF but completely dissolving in this solvent as reaction proceeds.

The selectivity in the reduction of 2-methylcyclohexanone by the reducing agents used runs parallel to that observed for 4-tert-butylcyclohexanone. The same sequence is found in the reductions of 3,3,5-trimethylcyclohexanone. This ketone has a methyl group in the C-3 axial position which severely hinders axial attack, and it is thus not surprising that the highest percentage of equatorial attack, resulting in an axial alcohol, occurs with bulky agents such as ZnH₂,

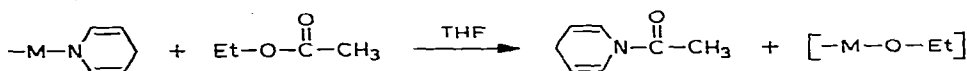
in vitro reductions by dihydropyridines [6–8].

ii. *Carboxylic acids.* Carboxylic acids are not reduced by the bis(1,4-dihydro-1-pyridyl) metal complexes. Organic acids, such as benzoic acid and stearic acid, protonate the nitrogen atom of the 1,4-dihydropyridyl moiety bound to the metal; 1,4-dihydropyridine is liberated from the complexes and the corresponding metal carboxylates are formed. Under these conditions 1,4-dihydropyridine slowly polymerizes.



iii. *Carboxylic esters.* Esters are usually reduced to alcohols, although some reductions to aldehydes and ethers are known.

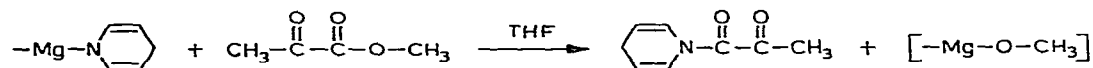
Ethyl acetate is not reduced when treated with an equimolar amount of either of the bis(1,4-dihydro-1-pyridyl)metal complexes in THF at room temperature. Instead, the 1,4-dihydropyridyl moiety bound to the metal is *N*-acylated:



This reaction is comparable with the reaction of carboxylic esters with amines, one of the known routes to amides [9]. It may, therefore, be concluded that in this type of reaction the amine character of the reactive 1,4-dihydropyridyl group bound to zinc or magnesium in the bis(1,4-dihydro-1-pyridyl)metal complexes predominates over its reducing ability. However, towards ethyl acetate there is a quantitative difference in reactivity between complex B and complex D, the latter reacting much the faster. The aminolysis of esters is generally considered to be a nucleophilic substitution at the carbonyl carbon atom [9]. This implies that the rate of reaction will depend, among other things, on the nucleophilicity of the amine. Since magnesium is more electropositive than zinc, the 1,4-dihydropyridyl groups in the magnesium complex are stronger nucleophiles than those in the corresponding zinc complex, which agrees with the observed differences in reactivity. In both complexes only one 1,4-dihydropyridyl group is reactive towards esters.

A qualitative difference in reactivity between the bis(1,4-dihydro-1-pyridyl)-zinc pyridine complex and its magnesium analogue is observed in the reactions with keto esters, e.g. the methyl ester of 2-oxo-propanoic acid (methyl pyruvate) and the methyl ester of 3-oxo-butanoic acid (methyl acetoacetate).

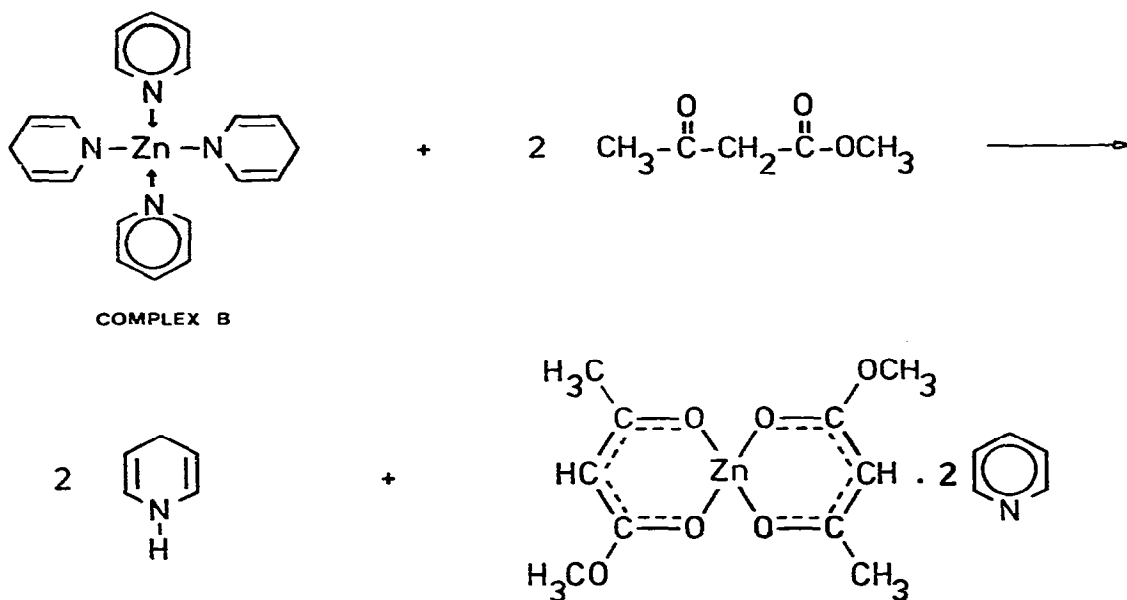
Complex B reduces methyl pyruvate to the methyl ester of 2-hydroxypropanoic acid (methyl lactate). Complex D, on the other hand, reacts with methyl pyruvate as with ethyl acetate, the 1,4-dihydropyridyl moiety attacking the α -keto ester at the ester carbonyl carbon atom:



This latter reaction also gives some reduction products, although in small quantities. In this connection we observed that 2,3-butanedione (biacetyl), which can only undergo a reduction, yields 3-hydroxy-2-butanone (acetoin) upon treat-

ment with either complex B or complex D followed by hydrolysis, complex B reacting faster than complex D.

Complexes B and D both react with the β -keto ester methyl acetoacetate (HMAA) with final formation of metal(MAA)₂ complexes. However, the routes to these products differ in the two cases. Methyl acetoacetate is liable to keto-enol tautomerism. Under the conditions used, complex B abstracts the enolic proton with formation of 1,4-dihydropyridine and Zn(MAA)₂ · 2 pyridine (Scheme 1).



Scheme 1. Reaction between the pyridine complex of bis(1,4-dihydro-1-pyridyl)zinc (complex B) and methyl acetoacetate in THF.

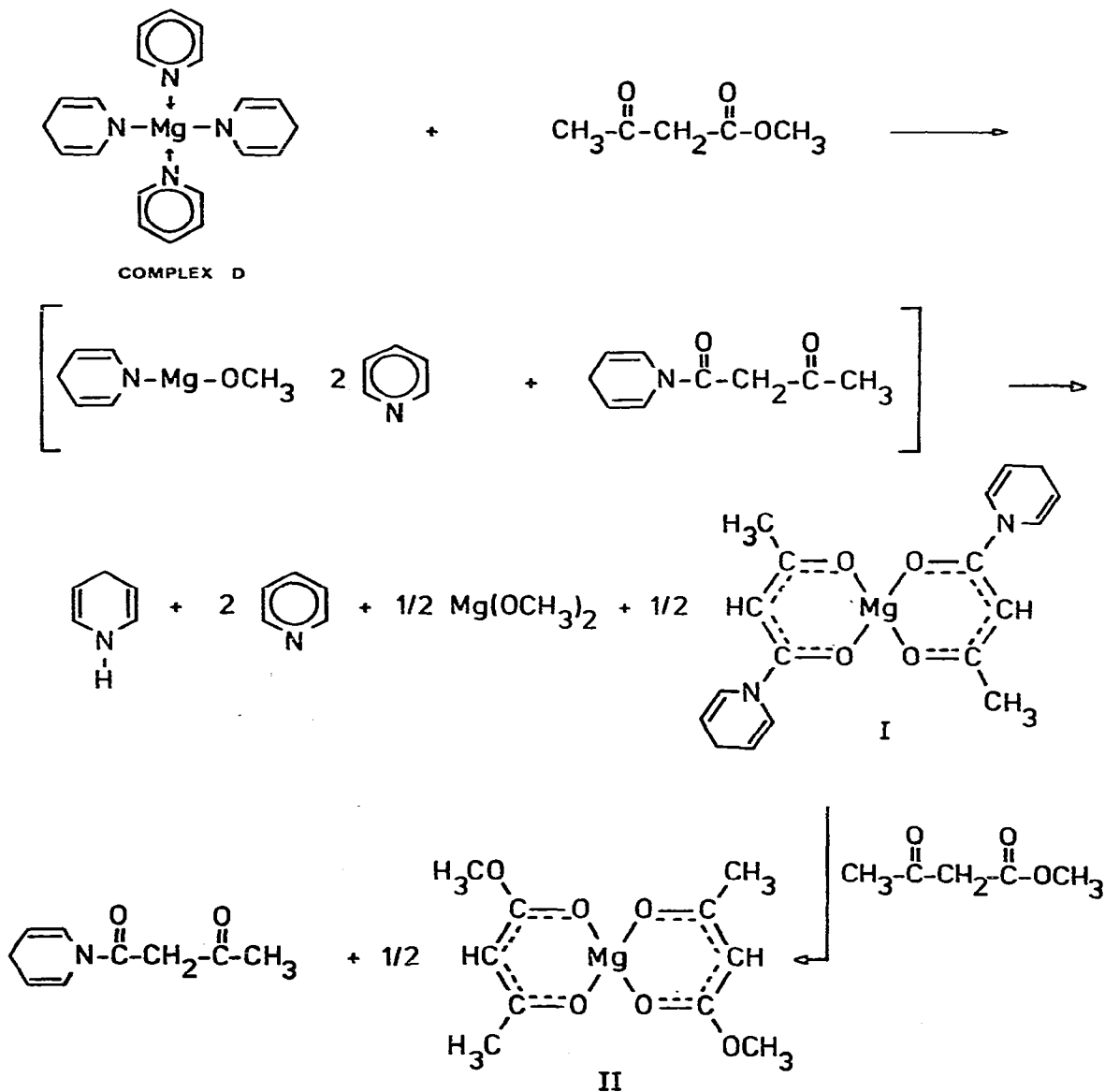
Similarly, when complex B is treated with two equivalents of 2,4-pentanedione (acetylacetonone, HAcAc), pyridine bis(acetylacetonato)zinc, Zn(AcAc)₂ · py, is formed. This compound was made by Graddon and Weeden [10] from aquo bis(acetylacetonato)zinc and pyridine. The structure of this presumably five-coordinate complex is not known but is probably similar to that of Zn(AcAc)₂ · H₂O, which has a geometry between trigonal bipyramidal and square pyramidal [11,12]. The zinc ion of Zn(MAA)₂ · 2 py is presumably six-coordinated. The increase of the coordination number of Zn^{II} in this complex relative to Zn(AcAc)₂ · py cannot be due to steric factors and is probably the result of the higher electronegativity of the chelating group, which leads to a more electron-deficient zinc centre. Hexacoordination of zinc in zinc β -diketonates has been observed in the complexes (PhZnAcAc)₂ · Zn(AcAc)₂ [13] and [(PhZnOPh) · Zn(Pac)₂]₂ [14].

In an equimolar reaction of complex D with methyl acetoacetate the first 1,4-dihydropyridyl group bound to magnesium attacks the substrate at the ester carbonyl carbon atom as in the reaction of complex D with ethyl acetate and methyl pyruvate. The enolic proton of the *N*-substituted-1,4-dihydropyridine formed reacts with the second 1,4-dihydropyridyl group bound to mag-

nesium with formation of 1,4-dihydropyridine. The magnesium complex I was isolated from the mixture (Scheme 2).

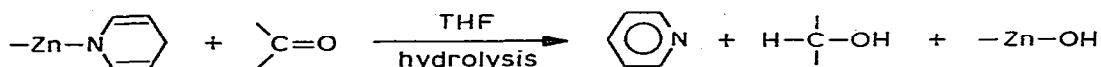
When I is treated with a second molar equivalent of methyl acetoacetate 1-(1,4-dihydropyridyl)-1,2-propanedione is liberated from the Mg^{2+} ion in a ligand exchange reaction and $Mg(MAA)_2$ is formed.

From the reactions with carboxylic esters it thus appears that complex D is very useful in the preparation of (novel)*N*-acyl-1,4-dihydropyridines. The scope and limitations of these reactions and the optimum conditions for the isolation and purification of the *N*-acyl-1,4-dihydropyridines are under investigation.

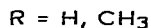
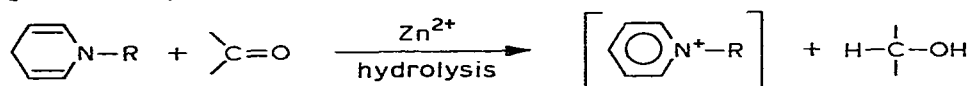


Scheme 2. Reaction between the pyridine complex of bis(1,4-dihydro-1-pyridyl)magnesium (complex D) and methyl acetoacetate in THF.

groups. This compound is also able to reduce carbonyl groups:



Under the same conditions 1,4-dihydropyridine itself does not react with ketones and aldehydes. Addition of zinc(II) to 1,4-dihydropyridines, however, promotes hydride transfer [16]:



The rate of this hydride transfer depends strongly on the solvent used. The reactions proceed best in apolar non-aromatic solvents such as pentane, hexane and cyclohexane. Such solvents do not at all compete with the carbonyl group of the substrate for a coordination site at the zinc ion. These experiments show that only when there is a bonding interaction, either a covalent or coordinate bond between zinc and the nitrogen atom of the 1,4-dihydropyridyl group, hydride transfer between this group and the substrate is promoted.

Within a ternary complex, containing enzyme, substrate and coenzyme, a direct hydride transfer occurs between the substrate and the 4-position of the nicotinamide ring of the coenzyme. However, there has been some dispute about whether direct hydride transfer occurs in an intermolecular concerted process or through a two-step process involving an initial electron transfer followed by a proton transfer. Moreover, the function of the zinc(II) ion in enzymatic catalysis has been a source of speculation and controversy, even after its definite location (through X-ray studies) near the reaction centre [17]. Although recent spectroscopic evidence points to a direct coordinative interaction between the catalytic zinc ion and the oxygen atom of the substrate [18–20], it is not clear whether or not there is an interaction between the zinc ion and the coenzyme. Competitive inhibition by chelating agents would seem to indicate such an interaction. On the other hand the X-ray data indicate the

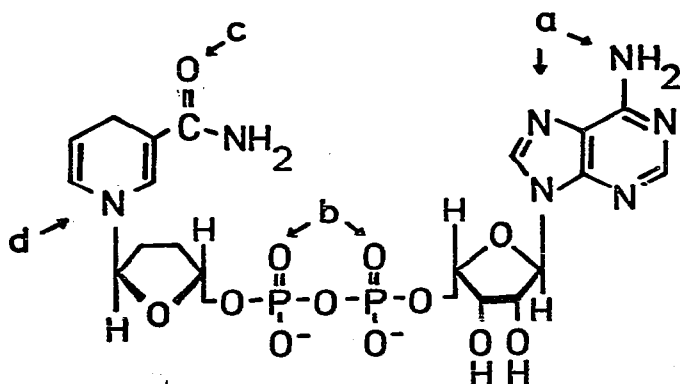


Fig. 1. NADH, nicotinamide adenine dinucleotide in the reduced form.

opposite, while spectroscopic evidence is contradictory [21].

When the reduced form of the coenzyme, NADH (Fig. 1), is considered, in principle four possibilities have to be considered for a coordinative coenzyme-metal ion interaction as indicated by Mildvan [22], who concludes that positions a and b are very unlikely on the basis of inhibition experiments. Mildvan also pointed out that it is "not apparent how coordination at c would facilitate hydride transfer; coordination at position d remains a possibility".

The reactions involving an interaction of the nitrogen atom of a 1,4-dihydropyridyl moiety with zinc, as described in this paper, may offer a clue to the understanding of the functioning of the metal ion in alcohol dehydrogenases. The mechanism of the reduction of a substrate by a 1,4-dihydropyridyl group directly bound to zinc, probably involving a one-electron transfer, is under investigation.

Experimental

General

All experiments were carried out under dry oxygen-free nitrogen. Solvents were carefully purified and dried, and then distilled and stored under nitrogen. Solvents, solutions and liquid reagents were handled with syringes.

¹H NMR spectra were recorded on Varian EM 390 and XL 100 spectrometers; the δ -values are believed to be accurate to ± 0.02 ppm.

A Hewlett Packard 5750 G gas chromatograph equipped with catharometer detector, and a Pye Chromatograph 104 with flame ionization detector were used for GLC analyses.

Starting materials

The preparations of the pyridine complexes of bis(1,4-dihydro-1-pyridyl)-zinc and -magnesium, and the TMED complex of bis(1,4-dihydro-1-pyridyl)-zinc, complex B, D and C respectively, were described in ref. 1.

Commercially available substrates were purified by distillation, sublimation or recrystallization. 2,2,6,6-Tetramethyl-trans-4-hepten-3-one was prepared as described by House and Weeks [23].

General procedure for reductions

To a stirred suspension of 10 mmol of the reducing agent (complex B, C or D) in 50 ml of THF at room temperature was added 10 mmol of the relevant unsaturated compound. After 24 hours the reaction was quenched with 0.5 ml of distilled water. 50 ml of pentane was added and the supernatant liquid decanted from the solid ($Zn(OH)_2$ or $Mg(OH)_2$). The solvent was evaporated off in vacuo (0–20°C, 15 mm), and the residue analyzed by NMR spectroscopy and/or GLC.

Reduction of cyclic ketones

The reductions were carried out in a 100 ml flask equipped with a magnetic stirrer. To a known amount of reducing agent (ca. 10 mmol) was added the appropriate volume of a 0.2 M solution of ketone in THF. The reactions were carried out at room temperature with a 1 : 1 ratio of reducing agent to ketone.

Distilled water was added after 24 hours. After filtration and evaporation of most of the solvent, the product mixtures were analyzed by GLC.

A 1.8 m × 2 mm 10% carbowax 20 M on chromosorb W column was used to separate the products from 4-*tert*-butylcyclohexanone (140°C), 3,3,5-trimethylcyclohexanone (110°C) and camphor (130°C). Products from the reaction of 2-methylcyclohexanone were separated on a 1.5 m × 2 mm 2% glycerol-2% 1,2,6-hexanetriol column at 65°C.

For the ketones used the order of elution was always the same; first the ketone was eluted, then the axial- or exo-alcohol, and finally the equatorial- or endo-alcohol. Relative retention times for each ketone, axial- or exo-alcohol and equatorial- or endo-alcohol, respectively, were as follows: 4-*tert*-butylcyclohexanone, 1.00, 1.20, 1.61; 2-methylcyclohexanone, 1.00, 2.72, 3.74; 3,3,5-trimethylcyclohexanone, 1.00, 1.67, 2.04; camphor, 1.00, 1.78, 2.01. The retention times varied slightly from column to column.

Reactions with carboxylic esters and α -keto esters

The following experiment is typical of the procedures utilized in the small-scale exploratory studies. To a suspension of 2.42 g (7.1 mmol) of complex D in 50 ml of THF stirring at room temperature was added 0.69 ml (7.1 mmol) of ethyl acetate. After 5 h stirring, 0.5 ml of distilled water was added followed by 50 ml of pentane. The liquid was decanted from the solid, and the solvent was evaporated off in vacuo (20°C, 2 mm). The residue was identified by ¹H NMR spectroscopy as *N*-acyl-1,4-dihydropyridine. In this compound hindered rotation about the amido C—N bond occurs, giving rise to separate signals for each of the protons at the 2-positions of the 1,4-dihydropyridyl moiety. These signals coalesce at 77°C in toluene-*d*₈.

¹H NMR chemical shifts (CDCl₃, 25°C): 2-protons, 7.12 (m) and 6.49 (m) ppm; 3-protons, 4.96 (m) ppm; 4-protons, 2.83 (m) ppm; —COCH₃, 2.13 (s) ppm.

Reactions with methyl acetoacetate

a. Complex B + methyl acetoacetate. To a stirred suspension of 4.25 g (11.1 mmol) of complex B in 50 ml of THF was added 1.90 ml (23.2 mmol) of methyl acetoacetate. The suspended solid dissolved immediately to give a clear colourless solution. The solvent was removed in vacuo and the white residue washed three times with pentane (3 × 50 ml). The white solid, Zn(CH₃COCHCO—OCH₃)₂ · 2 pyridine, was obtained in 80% yield after drying in vacuo. ¹H NMR chemical shifts (CDCl₃, 25°C), broad signals: —CH₃, 1.91 (s); —OCH₃, 3.61 (s); —CH, 4.80 (s); pyridine: 2-protons, 7.36 (m); 3-protons, 8.58 (m); 4-proton, 7.78 (m) ppm.

The mono pyridine complex of bis(acetylacetonato)zinc was obtained similarly from complex B and two molequivalents of acetylacetonate. ¹H NMR chemical shifts (CDCl₃, 25°C): —CH₃, 1.99 (s); —CH, 5.37 (s); pyridine: 2-protons, 7.43 (m); 3-protons, 8.57 (m) ppm; 4-proton, 7.86 (m) ppm.

b. Complex D + methyl acetoacetate. To a stirred suspension of 2.90 g (8.5 mmol) of complex D in 50 ml of THF was added 0.69 ml (8.5 mmol) of methyl acetoacetate. A brown suspension was formed. After 2 hours 0.5 ml of distilled water was added followed by 20 ml of pentane. After filtration the solvent was removed in vacuo and the white residue washed twice with pentane (2 ×

40 ml). After drying in vacuo $\text{Mg}(\text{CH}_3\text{COCHCONC}_5\text{H}_6)_2$ was isolated in 75% yield.

^1H NMR chemical shifts (toluene- d_8 , 100°C): $-\text{CH}_3$, 1.99 (s); $-\text{CH}$, 4.92 (s); 1,4-dihydropyridyl moiety: 2-protons, 6.87 (m); 3-protons, 4.63(m); 4-protons, 2.65 (m) ppm. Analysis, found: Mg, 6.88; N, 7.99; O, 17.32. $\text{C}_{18}\text{H}_{20}\text{MgN}_2\text{O}_4$ calcd.: Mg, 6.89; N, 7.94; O, 18.15%.

Two equivalents of methyl acetoacetate were added to a suspension of complex D in THF to give immediately a clear red solution with green fluorescence. After hydrolysis and evaporation of the solvent in vacuo, 50 ml of benzene was added to the residue to give a white suspension. After one hour the benzene layer was decanted from the solid and evaporated in vacuo (25°C , 1 mm), to give mainly $\text{C}_5\text{H}_6\text{NCOCH}_2\text{COCH}_3$. ^1H NMR chemical shifts (CDCl_3 , 25°C , keto form): $-\text{CH}_3$ 2.09 (s); $-\text{CH}_2$, 2.65 (s); 1,4-dihydropyridyl moiety: 2-protons, 7.08 (m) and 6.48 (m); 3-protons, 4.95 (m); 4-protons, 2.80 (m) ppm. In this case, the presence of two separate signals for the 2-protons of the 1,4-dihydropyridyl group indicates hindered rotation about the amido C—N bond. The white solid, $\text{Mg}(\text{CH}_3\text{COCHCOOCH}_3)_2$, was washed three times with pentane and dried in vacuo. ^1H NMR chemical shifts (CDCl_3 , 25°C): $-\text{CH}_3$, 1.78 (s); $-\text{OCH}_3$, 3.61 (s); $-\text{CH}$, 4.80 (s) ppm.

Acknowledgements

The authors wish to thank Mrs. H.J. Alberts-Jansen for able experimental assistance.

This investigation was supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for Advancement of Pure Research (ZWO).

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