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GRIGNARD REAGENTS AS POWDERS : PREPARATION AND REACTIVITY

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Abstract

The TDA-1 [$N(CH_2CH_2OCH_2CH_2OCH_3)_3$] chelating agent is able to complex Grignard reagents. This complexation leads to powders. The preparation is general and the complexes "RMgX/TDA-1" are easily prepared from every type of Grignard reagents. These solids are stable under nitrogen and can be titrated and used as Grignard reagents.

The study of their chemical reactivity shows a behaviour comparable to that of conventional Grignard reagents, the rate of reactions however being decreased. Selective addition onto a mixture of aldehyde and ketone is possible. Interestingly the reactions can be performed in hydrocarbon solvents (toluene, light petroleum, cyclohexane).

INTRODUCTION

Grignard reagents are amongst the most widely used reagents in organic chemistry (1,2). They are generally prepared and stored in solution, most commonly in "ethereal solvents". This aspect may be a considerable disadvantage and is the main limitation to their use at the industrial scale. We report here a method to get these reagents in the solid state: solid Grignard reagents may be obtained by precipitation from solution, using a chelating agent : the tris (dioxa 3,6 heptyl)amine or TDA-1 [$N(CH_2CH_2OCH_2CH_2OCH_3)_3$] (3).

This paper describes the preparation and the chemical behaviour of solid Grignard reagents in various solvents.

RESULTS

I - Preparation, physical properties and characterization of complexes "Grignard reagent/TDA-1 ".

The addition of a molar equivalent of TDA-1 in ether to an ethereal solution of two molar equivalents of Grignard reagent results in the formation of a pasty solid. After decantation, the solid may be recovered as a finely divided powder by removing the residual solvent under vacuum. This powder gives a positive test with Gilman's reagent (4) and can be titrated with an iodine solution in the same way as conventional Grignard reagents.

The preparation is effective for all types of Grignard reagent, and is easily performed under nitrogen using deoxygenated reagents. The Grignard reagents so prepared are listed in Table 1.

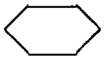
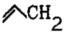
Table 1. Summary of "RMgX/TDA-1" complexes prepared from RMgX

nature of R halides	primary alkyl	secondary alkyl	tertiary alkyl	unsaturated	aromatic
Chloride	nBuCl		tBuCl	$PhCH_2Cl^*$	
Bromide	EtBr, nBuBr, iBuBr $nC_7H_{15}Br$, $nC_{16}H_{33}Br$	cHexBr iPrBr		$PhCH_2Br$ $CH_2{=}CH{-}CH_2Br$ $HC{\equiv}C{-}CH_2Br$ $CH_2{=}CHBr^*$	PhBr $p\text{-}CH_3O(C_6H_4)Br$ $m\text{-}CF_3(C_6H_4)Br$ $p\text{-}CF(C_6H_4)Br$ $p\text{-}F(C_6H_4)Br$
Iodide	MeI				

* Solvent THF

The "Grignard reagent /TDA-1" complexes described in this paper are soluble in THF but insoluble in ether, benzene, toluene, light petroleum and cyclohexane. They are stable at room temperature under nitrogen, thermal decomposition occuring only at temperatures ranging from 110 to 140°C in sealed reaction vessels under vacuum. (Table 2).

Table 2. Decomposition temperature of "RMgX/TDA-1" complexes

R	nBu		iBu		Ph
Decomp. temp.	110°C	110°C	110°C	120°C	140°C

^1H NMR spectra recorded in $THFd_8$ solution show a large upfield shift for the protons α to the magnesium atom (Table 3). Table 4 shows that the chemical shifts observed in the case of the complex "EtMgBr/TDA-1" are in good agreement with those of conventional Grignard reagents (5,6), and similar to those recently reported for a crown ether complexed reagent (7). The ratio of organic group R/TDA-1 could easily be determined from the ^1H NMR spectra of the complexes and was found to be 2/1 in every case.

Table 3. ^1H NMR chemical shifts of "RMgX/TDA-1" complexes in $THFd_8$.

complex	Hα to Mg atom	other protons	TDA-1
C_2H_5MgBr/TDA-1	-0.75, q, $2H(CH_2)$	1.15,t, $3H(CH_3)$	2.8-4.2 multiplet
$nC_6H_{13}MgBr$/TDA-1	-0.6, t, $2H(CH_2)$	1.2,multiplet, 11H (CH_2, CH_3)	2.7-4.1 "
$PhCh_2MgBr$/TDA-1	0.1, s, $2H(CH_2)$	7.1, multiplet, 5H (aromatics)	3-4.1 "
pF-PhMgBr/TDA-1		6.8, multiplet, 2H 7.6, multiplet, 2H	2.8-4,2 "
$mCF_3PhMgBr$/TDA-1		7.8, multiplet, 4H	2.7-4 "

Table 4. Comparison between the chemical shifts of various organometallic reagents in $THFd_8$.

Organometallic reagent	δ CH_3 ppm	δ CH_2ppm	Δ δ ppm δ CH_3- δ CH_2
EtMgBr/TDA-1	1.15	-0.75	1.90
EtMgBr(5)		-0.72	
Et_2Mg(5)		-0.77	
EtMgBr/TMEDA(6)	1.11	-0.78	1.89
*$NpMg(15\text{-}crown\text{-}5)^+$ (7)		-0.40	

*Np = neopentyl

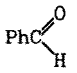
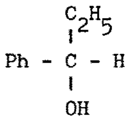
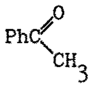
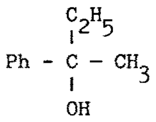
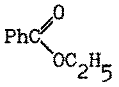
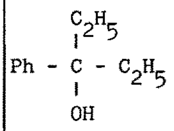
II REACTIVITY

The reactivity of the "RMgX/TDA-1" complexes towards different electrophilic reagents was studied in several solvents, especially in hydrocarbon ones.

1) Influence of the solvent on the reactivity of "RMgX/TDA-1" towards carbonyl compounds.

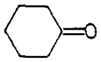
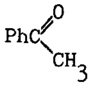
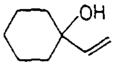
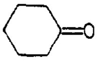
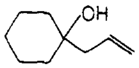
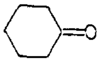
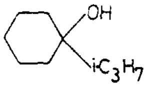
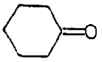
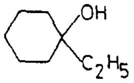
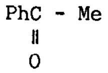
The reactivity of "EtMgBr/TDA-1" towards benzaldehyde, acetophenone and ethylbenzoate was investigated in several solvents (THF, Et_2O, toluene) at room temperature (Table 5). In every case the products were the same as those obtained with conventional Grignard reagents. The same yields were obtained in ethereal (Et_2O, THF) and hydrocarbon solvents (toluene). However in toluene the reaction occured more slowly and the difference in reactivity between aldehyde and ketone was less marked than in THF. Representative results in toluene with a range of reagents are shown in table 6. Further experiments were performed in light petroleum or cyclohexane Reaction at room temperature was very slow. However satisfactory yields of pure products could be obtained by refluxing for 4 hours, (table 7). In every case the yields were again comparable to those obtained with conventional Grignard reagents.

Table 5. Reaction of "EtMgBr/TDA-1" with carbonyl compounds in different solvents at 20°C.

carbonyl compound	solvent	time	product	yield* %
	THF	5 min	 $Ph-\overset{C_2H_5}{\underset{OH}{C}}-H$	90
	Et_2O	15 min		81
	toluene	2h30		86
	THF	1h	 $Ph-\overset{C_2H_5}{\underset{OH}{C}}-CH_3$	78
	Et_2O	3h		80
	toluene	5h		74
	THF	1h	 $Ph-\overset{C_2H_5}{\underset{OH}{C}}-C_2H_5$	100
	toluene	5h		83

* isolated products

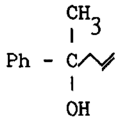
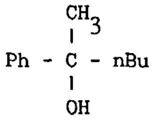
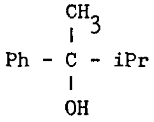
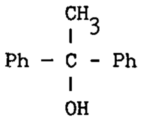
Table 6. Reaction of "RMgBr/TDA-1" with carbonyl compounds in toluene at room temperature during 5 h.

R	carbonyl compound	product	yield %*
CH_2=CH-	PhCHO $nC_7H_{15}CHO$   $\mathrm{PhC(=O)CH_3}$	PhCH(OH)  $nC_7H_{15}CH(OH)$  $Ph(CH_3)C(OH)$	92 89 81 83
CH_2	PhCHO $nC_7H_{15}CHO$ 	PhCH(OH) $nC_7H_{15}CH(OH)$ 	80 71 75
iPr	PhCHO $nC_7H_{15}CHO$ 	PhCH(OH)iPr $nC_7H_{15}CH(OH)iPr$ 	65 69 33
Et			61
Me	PhCHO	PhCH(OH)Me	95
Ph**	 $\mathrm{PhC(=O)-Me}$	$Ph_2CMe(OH)$	75

* yield in isolated products

** 1 hour at 65°C

Table 7. Reaction of acetophenone with "RMgX/TDA-1" in light petroleum at 65°C during 4h.

R	product	yield* %
	 $Ph-\overset{CH_3}{\underset{OH}{C}}$	100
nBu	 $Ph-\overset{CH_3}{\underset{OH}{C}}-nBu$	82
iPr	 $Ph-\overset{CH_3}{\underset{OH}{C}}-iPr$	60
Ph**	 $Ph-\overset{CH_3}{\underset{OH}{C}}-Ph$	76

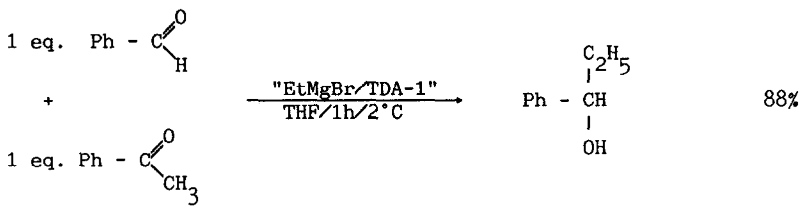
* isolated products

** the same result was obtained in cyclohexane.

2) Selectivity of "RMgX/TDA-1" complexes towards a mixture of aldehyde and ketone.

Since the "RMgBr/TDA-1" complexes are less reactive than conventional Grignard reagents, the selectivity of the addition reaction of "EtMgBr/TDA-1" towards an equimolecular mixture of benzaldehyde and acetophenone was studied. The best results were obtained in THF at 2°C over a period of 1 hour. (reaction 1).

Réaction 1



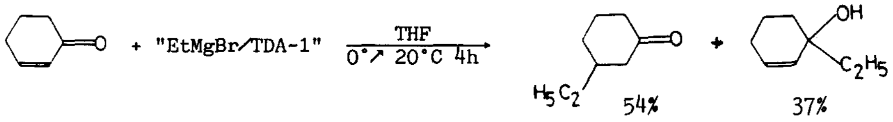
Less than 6% of 2-phenyl 2-butanol was obtained and 83% of the acetophenone was recovered unreacted. This degree of selectivity is comparable to that obtained with either organocuprates (8 9) or organomanganese derivatives (10) at low temperature.

3) Reaction of "RMgX/TDA-1" complexes towards other electrophiles

The following results illustrate the reactivity of "RMgX/TDA-1" complexes with various reagents (reactions 2-7).

- cyclohexen-2 one : the reaction of "EtMgBr/TDA-1" with cyclohexen-2 one gave a mixture of the 1,2 addition (37%) and the 1,4 addition product (54%). The reaction was carried out in THF at 0°C and the temperature allowed to rise to 20°C over a period of 4h (reaction 2)

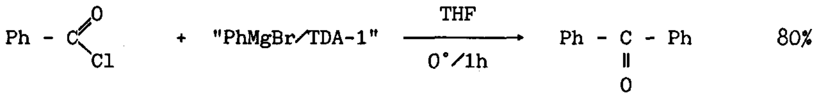
Réaction 2



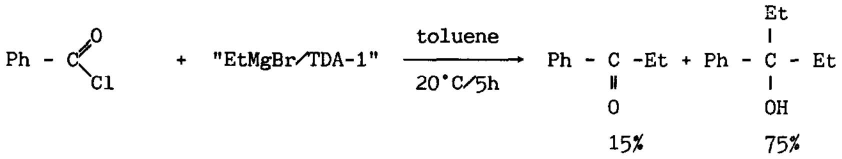
Conventional ethylmagnesiumbromide gave almost opposite proportions (11)

- benzoyl chloride : ketone was obtained in good yield by reaction of the "PhMgX/TDA-1" complex with benzoyl chloride in THF (reaction 3). In other solvents, for example toluene, the reaction was less selective and a mixture of ketone and tertiary alcohol was obtained (reaction 4).

Reaction 3



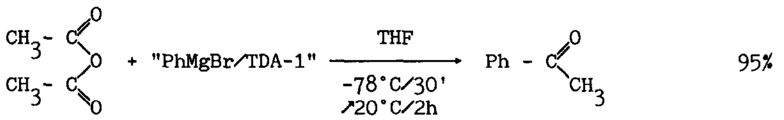
Reaction 4



A similar result has been obtained with conventional Grignard reagents at -78°C (12)

- acetic anhydride : the "PhMgBr/TDA-1" complex reacted with acetic anhydride to give acetophenone in good yield (reaction 5)

Reaction 5



The conditions are milder than those required with conventional Grignard reagents (13).

- ethylchloroformate : the "RMgX/TDA-1" complex reacted with ethychloroformate to give esters in good yield (Table 8). The results are similar to those obtained with conventional Grignard reagents (14).

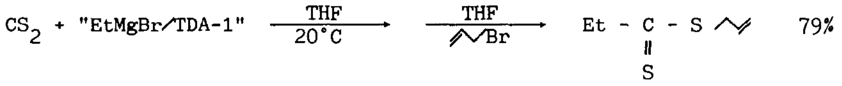
Table 8. Reactivity of $ClCO_2Et$ towards "RMgX/TDA-1"

R	solvent	conditions		product	yield %*
nHept	Et_2O	0°C	3h	nHept-C(=O)-OEt	45
Ph	Et_2O	0°C	3h	$PhCO_2Et$	45
Ph	THF	-15°C	1h	$PhCO_2Et$	94

* isolated product

- carbon disulfide : the reaction of EtMgBr with CS_2 has been reported in the literature (15). The reaction using "EtMgBr/TDA-1" (reaction 6) gave similar results.

Reaction 6



- silicon compounds : no reaction was observed between Me_3SiCl and "RMgX/TDA-1". This contrasts with the reaction observed with the hexacoordinated dianonic silicon complex, sodium tris(benzene-1,2 diolato)silicate (Table 9) (reaction 7) which gives the same results as those observed with conventional Grignard reagents (16).

Reaction 7

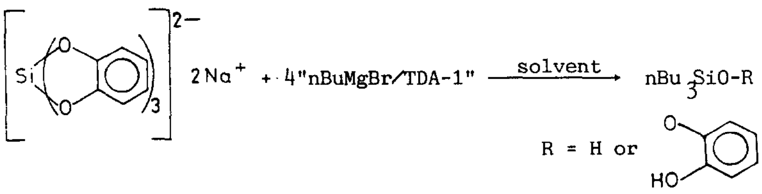
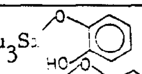
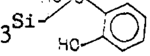


Table 9. Reaction of "nBuMgBr/TDA-1" with sodium tris(benzene-1,2 diolato) silicate

Grignard reagent	solvent	T°C	Time(h)	Product (yield %)*
nBuMgBr	Et_2O	35	2	nBu_3Si  82
"nBuMgBr/TDA-1"	Et_2O	20	5	nBu_3Si  83
nBuMgCl	THF	15	12	nBu_3SiOH 66
"nBuMgBr/TDA-1"	THF	20	5	nBu_3SiOH 61

* isolated products

CONCLUSION

The complexation reaction of Grignard reagents with TDA-1 leads to stable and easily handled solid organometallic reagents. They can be prepared from every type of Grignard reagent and have a chemical behaviour similar to classical ones although with a lower reactivity. However it is possible to carry out a selective addition reaction on a mixture of aldehyde and ketone. The reactions may be performed in hydrocarbon solvents, thus avoiding the use of ethyl ether or THF.

EXPERIMENTAL

Preparation of the "RMgX/TDA-1" complex

Reactions were carried out under nitrogen. Solvents were dried, distilled and deoxygenated. Starting materials were commercial or were prepared by literature methods.
IR spectra were recorded with a Perkin-Elmer 298 spectrophotometer, ^1H NMR spectra with a Varian EM 360 spectrometer. Chemical shifts, δ, are relative to TMS.
All the compounds described in this paper were identified by the usual techniques and compared with authentic samples.

Grignard reagents as powders were prepared from Grignard reagents in solution either in ether or in THF.

The preparation of "EtMgBr/TDA-1" (ethereal solution) and "⁄\MgBr/TDA-1" (THF solution) are given as examples.

- Preparation of "EtMgBr/TDA-1"

A solution of 23 mmoles (7.5g) of TDA-1 in 75ml of cyclohexane was added dropwise to a vigorously stirred ethereal solution of 46.5 mmoles of EtMgBr (75ml of a 0.65 M solution). A white precipitate was immediately formed. The reaction mixture was stirred for 1 hour, then decanted for 2 hours. The solid was filtered and the residue was then dried under vacuum during 2 hours. 20.25g of "EtMgBr/TDA-1" complex were obtained. It was titrated with a solution of iodine in toluene : 1.64 mmoles of ethyl group were present in 1g of powder. The yield was 72%.

- preparation of "⁄\MgBr/TDA-1"

50 mmoles of ⁄\MgBr (50ml of a 1M solution in THF) were placed in a Schlenk tube. Half of the solvent was evaporated under vacuum, then 25 mmoles (8g) of TDA-1 in 50ml of cyclohexane were added dropwise to the vigorously stirred Grignard solution. During the addition a white precipitate was formed and dissolved soon. The mixture was then stirred during 1 hour. Two layers were formed. After decantation, 50ml of cyclohexane were added to the lower layer, a solid precipitated. It was filtered and dried under vacuum. The pasty solid was washed with 50ml of

ether, filtered and dried under vacuum for 2h. 14.9g of "/\MgBr/TDA-1" complex were obtained. Titration indicated the presence of 2.15 mmoles of vinyl group for 1g of complex. The yield was 64%.

Reactions of "RMgX/TDA-1" complexes

Two types of procedures were used depending on the nature of the solvent.

i) when the reaction was performed in THF, the "RMgX/TDA-1" complex in solution in THF was added to the reagent.

ii) when the reaction was performed in another solvent (ether, light petroleum, cyclohexane or toluene), the reagent was added to a suspension of the Grignard in the solvent.

All the compounds were purified by column chromatography on silicagel. We report here one example for each type of procedure.

Reaction in THF : reaction of "EtMgBr/TDA-1" with benzaldehyde.

5 mmoles (0.53g) of benzaldehyde diluted in 10ml of THF were placed in a three- necked flask at 20°C. 5.5mmoles of "EtMgBr/TDA-1" dissolved in 10ml of THF were added dropwise. The reaction was checked by gpc. When the reaction was complete, the mixture was hydrolysed with a satured solution of NH_4Cl. The product was extracted with ether. The combined organic layers were washed twice with brine, then dried over $MgSO_4$. After evaporation of the solvent, the crude product was chromatographed on silicagel and was eluted with pentane/dichloromethane 50/50. The product was isolated and characterized (IR, ^1H NMR) by comparison with an authentic sample. The purity was checked by gpc. 0.61g (90%) of 1-phenyl 1-propanol were obtained.

Reaction in ether, light petroleum, cyclohexane or toluene : reaction of "EtMgBr/TDA-1" with benzaldehyde in toluene is given as example.

6.37g of "EtMgBr/TDA-1" (8.98mmoles) were suspended in 18ml of toluene at 20°C. 0.85g (8mmoles) of benzaldehyde dissolved in 18ml of toluene were added dropwise to the stirred suspension. The reaction was checked by gpc. When the reaction was complete, the product was isolated as precedently 0.94g (86%) of 1-phenyl 1-propanol were obtained.

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