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Active Metals Prepared in Liquid Ammonia. Zinc and Tin-Promoted Synthesis of β-Hydroxyesters, Homoallylic and Homopropargylic Alcohols

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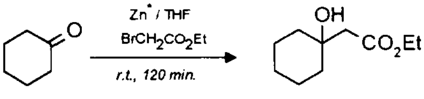
Abstract: Active zinc and tin powder can be prepared by reduction of $ZnCl_2$ and $SnCl_2$ with sodium in tetrahydrofuran-liquid ammonia mixtures of various compositions. The activity of the reduced zinc depends on concentration of ammonia in the reaction medium. Zinc (A) prepared in liquid ammonia (Method A) was much less active then zinc (B) prepared in THF containing 10-20 volume % of liquid ammonia (Method B). The X-ray powder diffractometry data suggested that zinc (B) was less crystalline then zinc (A). The Reformatsky and Barbier type reactions of carbonyl compounds with α-bromoesters, allylic and propargylic bromides in the presence of Zn or Sn prepared by method B gave the corresponding β-hydroxyesters, homoallylic and homopropargylic alcohols in good to excellent yields. Copyright © 1996 Elsevier Science Ltd

Active metals are widely applied in organic synthesis.[1] Particularly great attention has recently been directed toward application of active zinc and tin in the Reformatsky and Barbier type reactions.[2] There are many methods of production of these metals in active forms, most of them are based on the reduction of anhydrous salts with an ethereal solution of preformed lithium naphthalenide (Rieke method),[3] or with solid potassium-graphite intercalate.[4] These methods have some disadvantages: necessity to use electron transferring agents (naphthalene or biphenyl) which must be subsequently separated, inconvenience of preparation of graphite-potassium etc.

It is well known that solutions of alkali metals in liquid ammonia are strong reducing agents widely used for reduction of organic and inorganic compounds.[5] There are many examples of reduction of metal salts with such solutions.[6] It was reported that zinc metal of 98.1 ÷ 99.3 % purity could be prepared *via* reduction of zinc cyanide with sodium in liquid ammonia.[7] On the other hand, there are no reports on the possibility of using this system for preparation of active zinc suitable for applications in organic reactions. Taking into account the low price of sodium metal and ammonia and also attractiveness of this solvent we have attempted to use these conditions for the generation of active zinc. A preliminary report on the use of zinc prepared in liquid ammonia in the Barbier reaction was published.[8]



1a

Scheme 1

The most important application of active zinc in organic synthesis is for the Reformatsky reaction - where the activity of zinc is of crucial importance.[9] Thus, we consider that the reaction of ethyl bromoacetate with cyclohexanone (room temperature, 120 min.) should be a good criterion of zinc activity (Scheme 1).

After some preliminary experiments we have found that the most convenient way to carry out the reduction of zinc chloride was portionwise addition of sodium to a suspension of anhydrous $ZnCl_2$ in liquid ammonia at -78 °C. When the moderately exothermic reaction ceased (5-15 min. at -78 to -33 °C) anhydrous tetrahydrofuran was added to a black suspension of metallic zinc and the mixture was refluxed in order to remove ammonia (Method A). Zinc powder prepared in this way was, however, of low activity and its application in Reformatsky reaction gave yields around 50%. It appeared to us that the low activity of the Zn powder could have been due to a possible crystallization of the metal when it was precipitated from the solution in liquid ammonia, although the solubility of zinc in ammonia was reported to be negligible.[5] In a series of experiments the reduction was carried out in tetrahydrofuran-liquid ammonia mixtures of various compositions. Whereas in pure tetrahydrofuran the reduction did not occur, the presence of 10-20 volume % of liquid ammonia assured a rapid reduction at -33 °C (Method B). The zinc generated according to this method assured high yield of the Reformatsky reaction between ethyl bromoacetate and cyclohexanone, comparable to that obtained with Rieke-Zn™ and zinc-graphite.[2b, c]

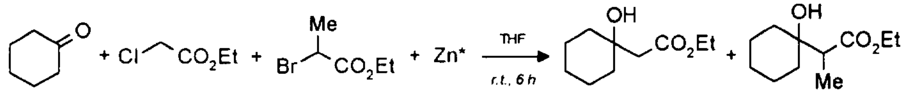
Substitution of sodium with lithium had no effect on the activity of zinc prepared, but use of barium and calcium resulted in inferior yields of **1a**, or even in incomplete reduction of $ZnCl_2$. The activities of the fine black suspension of metallic zinc powder prepared from $ZnCl_2$ and $ZnBr_2$ insoluble[5] in liquid ammonia were similar. Curiously, and contrary to our expectations, reduction of zinc cyanide which is soluble in ammonia,[5] with a solution of sodium (homogeneous conditions) gave zinc as macrocrystalline solid together with a metallic mirror. Application of zinc prepared in this way in the model reaction (Scheme 1) failed to afford the β-hydroxyester **1a**. Recently, we have reported a preliminary finding that the Barbier reaction of carbonyl compounds and allylic bromides could be carried-out in liquid ammonia medium.[10] Contrary to that observation, when a solution of cyclohexanone and ethyl bromoacetate was added to a suspension of zinc (B) in liquid ammonia no β-hydroxyester (**1a**) was formed.

According to method B tin(II) chloride can be reduced to tin powder. In this case it was necessary to use 25-30 volume % of liquid ammonia in tetrahydrofuran for the efficient reduction. The zinc and tin powders prepared by method B were sufficiently active for the Reformatsky and Barbier reaction. In further preparative work zinc and tin prepared *via* procedure B was used (Table 1).

$$\underset{\mathbf{2}}{n\text{-}C_8H_{17}\text{-}Br} \xrightarrow{Zn^*/THF} \underset{\mathbf{3}}{n\text{-}C_8H_{17}\text{-}ZnBr}$$

Scheme 2

The conditions for preparation of active zinc according to procedure B were optimized using 1-bromooctane (**2**) as the model substrate (Scheme 2). Formation of the organozinc compound (**3**) was monitored by GC and was based on the *n*-octane peak after hydrolysis with dilute HCl solution. Unfortunately, all attempts to improve the activity of zinc met with little success (Table 2). The most reactive zinc prepared in liquid ammonia according to method B was insufficiently active to effect the reaction with α-chloroesters and alkyl bromides whereas Rieke-Zinc™ assures yields of 60-100 %.[2a, b, 3a]

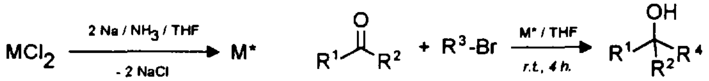


1.25 mmol *1.5 mmol* *1.5 mmol* *3.0 mmol* **1a**, 0% **1b**, 80 %

Scheme 3

On the other hand, a selective Reformatsky reaction of α-bromoesters (but not of chloroesters) with carbonyl compounds could prove to be of some synthetic advantage in certain cases. A competitive experiment revealed this selectivity (Scheme 3). An equimolar mixture of ethyl chloroacetate and ethyl α-bromopropionate was stirred in the presence of cyclohexanone and active zinc (B) in THF at room temperature for 6 hours.

Table 1. Reformatsky and Barbier-Type Rections Promoted by Active Zinc and Tin Prepared by Method B



Entry	Metal M*	R^1	R^2	R^3	R^4	Yield (%)
a	Zn	$-(CH_2)_5-$		$-CH_2CO_2C_2H_5$	$-CH_2CO_2C_2H_5$	96
b	Zn	$-(CH_2)_5-$		$-CH(CH_3)CO_2C_2H_5$	$-CH(CH_3)CO_2C_2H_5$	82
c	Zn	C_6H_5-	H-	$-CH_2CO_2C_2H_5$	$-CH_2CO_2C_2H_5$	90
d	Zn	$3,4,5-(CH_3O)_3C_6H_2-$	H-	$-CH_2CO_2C_2H_5$	$-CH_2CO_2C_2H_5$	72
e	Sn	C_6H_5-	H-	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$	93
f	Sn	$n-C_7H_{15}-$	H-	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$	86
g	Zn	$n-C_6H_{13}-$	CH_3-	$-CH_2CH=CH_2$	$-CH_2CH=CH_2$	96
h	Zn	C_6H_5-	H-	$-CH_2CH\equiv CH$	$-CH_2CH\equiv CH$	83
i	Zn	C_6H_5-	H-	$-CH_2CH=CH-CO_2CH_3$	$-CH(CO_2CH_3)CH=CH_2$	61

[a] Yields of isolated produtcs. [b] Mixture of the homopropargylic alcohol (R^4 = $-CH_2CH\equiv CH$, **1h**) and the α-allenic alcohol (R^4 = $-CH=C=CH_2$) in the ratio 91:9 as determined by GC. [c] The diastereoisomeric ratio determined by GC was 43:57.

Table 2. Comparison of the Activity of Variously Prepared Zinc in Reaction with 1-Bromooctane[a]

ZnX_2	Alkali Metal	Solvent ($C_{ammonia}$ vol. %)	Yield of 3 (%)[b]
$ZnCl_2$	Na	THF (15)	20
$ZnCl_2$/THF[c]	Na	NH_3 (100)	5
$ZnCl_2$	Na	DME (25)[d]	24
$ZnCl_2$	Na	Et_2O (15)	13
$ZnCl_2$	Na	Toluene (25)	10
$Zn(CN)_2$	Na	THF (15)	1
$ZnCl_2$	K	THF (15)	35
$ZnCl_2$	Li	THF (15)	41
Rieke-Zn™; Ref. 3a			100

[a] After evaporation of ammonia according to procedure B, Zn* (3.75 mmol) was reacted with 1-bromooctane (3.12 mmol) in an appropriate solvent (30 mL), rt, 20 h. [b] The yield was determined by GC after hydrolysis with a dilute HCl solution. [c] The solution of $ZnCl_2$ in THF was added dropwise to a solution of sodium in liquid ammonia (30 mL). [d] DME = 1,2-dimethoxyethane

The reaction was highly selective: 80% of the product (**1b**) derived from α-bromopropionate was formed whereas of the reaction with chloroester did not occurs.

One could suppose that zinc generated in liquid ammonia could be covered with amide layers similar to passivation of zinc in aqueous media. However, differences in activity of Zn obtained according to procedures A and B cannot be explained in this way. We have initially suspected that during the reduction in liquid ammonia partial crystallization could occur, which would decrease the metal surface and consequently its activity.

The samples prepared according to the procedure A or B were investigated by electron microscopy (SEM), energy dispersive X-ray (EDX) and X-ray powder diffractometry.

Microscope pictures of Zn samples A and B showed light, poorly developed structures with the diameter range of 0.2 to 2 μm. It was difficult to see differences in diameter or in degree of agglomeration between these samples. We performed many EDX microanalyses - both for small and big grains, placed in dark or light regions. In each analysis the presence of the same elements was confirmed - mostly Na, Cl, Zn, O and trace amounts of C, Si, Cu. Microanalysis of the dark region showed relatively higher amount of C and Zn. Unfortunately because of low detector sensitivity, we could not observe the presence of nitrogen, that was expected in the form of amide or imide groups linked to the Zn surface. On the basis of the obtained low-resolution SEM pictures we could not calculate the size of the Zn crystallites. According to the EDX microanalyses performed for even 5000× magnification, we could not distinguish between separate crystalline Zn and NaCl phases. The observed structures, in the range of micrometers, are agglomerates of more subtle, well-intermixed microcrystallites of Zn and NaCl.

From the X-ray powder diagrams for both Zn samples the same phase composition was found (Table 3). In both samples neither Na_2ZnCl_4, nor zinc chloride, nor sodium amide was detected. In the case of the powder diagram of sample B relative intensities of peaks originating from Zn were lower and broader comparing to the diagram of sample A. Peaks originating from the halite (NaCl) in the both samples had similar intensities and widths. Lower intensity and higher value of the peak width from the crystalline phase of zinc in sample B indicated that the metal prepared by this procedure was significantly *less crystalline* than zinc prepared according to the procedure A.[11] However it was difficult to estimate the metal crystallite sizes in both samples.

Table 3. X-Ray Diffraction Data of Zn/2NaCl System Obtained by Method A and B

d_{obs} (nm)	Phase	Relative Intensity, I_{obs} (%) / Half-height Width (mm)			
		Zinc (A)	Zinc (B)	Zinc (A)[a]	Zinc (B)[a]
0.3250	NaCl	12 / 3	10 / 3	15 / 3	10 / 3
0.2814	NaCl, ZnO	100 / 3	100 / 3	100 / 3	100 / 3
0.2602	ZnO	3 / 6	5 / 27	5 / 8.5	8 / 22
0.2467	Zn, ZnO	10 / 9	8 / 24	10 / 11	8 / 18
0.2306	Zn	8 / 4	3 / 10	5 / 6	none
0.2084	Zn	25 / 6	8 / 12	18 / 6	none
0.1990	NaCl, ZnO	50 / 3	50 / 3	50 / 3	50 / 3
0.1698	NaCl	2 / 4	1 / 4	3 / 5	—[b]
0.1683	Zn	4 / 9	none	3 / 9	—[b]
0.1625	NaCl, ZnO	15 / 4	15 / 4	20 / 4	—[b]
0.1408	NaCl, ZnO	6 / 5	5 / 5	10 / 4	—[b]

[a] Samples were stored in the ambient atmosphere for 72 hours.[b] Not measured.

Significant differences have been detected in the X-ray powder data obtained for Zn(A) and Zn(B) samples after keeping them for 72 hours in the ambient atmosphere. In the sample Zn(A) only small decrease of relative peak intensities originating from Zn and small increase in peak intensities originating from the ZnO phase were found. In the sample B significant changes were observed for the same peaks: the zinc phase nearly completely disappeared (Table 3). The results indicated that the Zn sample prepared according to the procedure B considerably differed from the Zn sample prepared according to the method A. The differences could result from the different values of surface areas and surface energies. However, from the low-resolution SEM pictures of both samples it appeared that were agglomerates of similar size there and it was difficult to compare the surface character of both samples.

On the basis of the results obtained from the X-ray powder data it could be assumed that the lower activity of Zn(A) could be attributed to the loss of the developed active structure and to the increase of the crystallites size due to partlial recrystallization during the reduction and slow evaporation of the liquid phase i.e. ammonia. Additionally, for all the Zn samples, there could be surface deactivation due to the chemisorption of ammonia.

In conclusion, a practical new method for generating active zinc and tin in liquid ammonia has been established. The Reformatsky and Barbier type reactions of carbonyl compounds with α-bromoesters and with allylic and propargylic bromides, worked well with these active metals and gave the corresponding β-hydroxyesters, homoallylic and homopropargylic alcohols in good to excellent yields. Although the activity of the metal was lower then the corresponding Rieke-Zinc™, the remarkably safe and short procedures and the low cost should render this approach particularly attractive for larger-scale applications.

Experimental Part

General. ^1H NMR spectra were recorded in chloroform-*d* with Varian GEMINI-200 spectrometer (200 MHz). Chemical shifts are given in δ units relative to TMS. IR spectra were recorded with a Perkin-Elmer FTIR 1640 spectrophotometer. GC analyses were performed on Shimadzu GC-14A chromatograph. GC-MS analyses were performed with Hewlett Packard HP 5972A MSD unit. Scanning electron microscopy pictures (SEM) and energy dispersive X-ray analyses (EDX) were conducted with EM Jeol JSM-35, with W-filament electron source, working at 20 kV, equipped in EDX LINK ISIS Microanalysis System, with LINK PENTAFET detector. X-Ray powder diagrams for phase analysis of Zn samples were prepared by DRON X-Ray Diffractometer with Fe(Mn filter) X-ray source operating at 20 kV voltage and 14 mA current, vertical slits 1-1-0.5 and horizontal Soller slits 2×2.5°.

Reactions were carried-out under purified grade argon atmosphere. Technical grade ammonia was purified before condensation by passing through a column of granular potassium hydroxide. Tetrahydrofuran was freshly distilled before use from potassium/benzophenone under purified argon atmosphere. Commercially available tin(II) chloride (POCh, p.a.) was dried before use by heating at ca. 200°C for 6 hours. Zinc chloride (Fluka, p.a.) was fused before use.

Preparation of β-Hydroxyesters, Homoallylic and Homopropargylic Alcohols. Method B. To a 50 mL round-bottom flask equipped with a magnetic stirrer, dropping funnel and dry-ice condenser (protected by a drying tube filled with granular KOH) and charged with crushed anhydrous zinc chloride (0.511 g, 3.75 mmol) or anhydrous tin(II) chloride (0.711 g, 3.75 mmol) liquid ammonia (5 mL for $ZnCl_2$ and 10 mL for $SnCl_2$) was condensed. To the stirred suspension tetrahydrofuran (30 mL for $ZnCl_2$ and 20 mL for $SnCl_2$) was added throught the septum inlet in one portion at -78°C and freshly cut sodium metal (0.157 g, 7.6 mmol) was transferred to the flask maintaining argon blowing over the neck of the flask. After stirring for additional 15 min. at -33°C the ammonia was evaporated. The black slurry was refluxed for 45 min. and then α-bromoester, allyl or propargyl halide (3.0 mmol) and carbonyl compound (2.0 mmol) in THF (5 mL) were added at 20°C. After stirring for 120÷240 min. saturated aqueous NH_4Cl was added to the mixture. The aqueous layer was extracted with ether (4×20 mL), the combined organic phase washed twice with brine (20 mL). The solvent was removed *in vacuo* and the crude product was purified by short-path distillation or flash chromatography (silica gel, hexane - ethyl acetate: 4/1 v/v).

Ethyl 2-(1-hydroxycyclohexyl)acetate (1a). Bp 100-102°C/7 Torr (Lit.[9a] bp 86-89°C/2 Torr).

Ethyl 2-(1-hydroxycyclohexyl)propionate (1b). Bp 80°C (oven temperature)/0.3 Torr (Lit.[12] bp 125-127°C/12 Torr).

Ethyl 3-phenyl-3-hydroxypropionate (1c). Bp 80°C (oven temperature)/0.1 Torr (Lit.[9a] bp 151-154°C/11-12 Torr).

Ethyl 3-(3,4,5-trimethoxyphenyl)-3-hydroxypropionate (1d). Mp 56-57°C (Lit.[13] mp 57-58°C); IR (KBr) cm^{-1} 3476, 1735; ^1H NMR ppm 1.28 (3H, t, J = 7 Hz), 2.73 (2H, m), 3.35 (1H, br. s), 3.83 (1H, s), 3.86 (6H, s), 4.20 (2H, q, J = 7 Hz), 5.03-5.13 (1H, m); MS (EI) *m/z* (relative intensity, %) 284 ($M^{+\bullet}$, 50), 266 (0.5), 239 (11), 197 (95), 169 (100), 154 (33), 138 (36).

1-Phenylbut-3-en-1-ol (1e). Bp 70°C (oven temperature)/0.8 Torr (Lit.[14] 111-112 / 13 Torr).

Undec-1-en-4-ol (1f).[2d] IR (neat) cm^{-1} 3356, 3076, 1641; ^{1}H NMR ppm 0.88 (3H, t, J = 6 Hz), 1.10-1.65 (13H, m), 2.00-2.30 (2H, m), 3.62 (1H, m), 5.10-5.20 (2H, m), 5.76-5.92 (1H, m); MS (EI) *m/z* (relative intensity, %) 129 (M-$C_3H_5^+$, 20), 111 (15), 83 (6), 69 (100), 55 (38).

4-Methyldec-1-en-4-ol (1g).[2e] IR (neat) cm^{-1} 3384, 3075, 1640; ^{1}H NMR ppm 0.89 (3H, t, J = 6.5 Hz), 1.16 (3H, s), 1.29-1.52 (11H, m), 2.22 (2H, d, J = 7.5 Hz), 5.06-5.16 (2H, m), 5.76-5.97 (1H, m); MS (EI) *m/z* (relative intensity, %) 129 (M-$C_3H_5^+$, 38), 113 (4), 85 (20), 69 (46), 55 (21).

1-Phenylbut-3-yn-1-ol (1h). Bp 40°C (oven temperature)/0.15 Torr (Lit.[15] 72°C/0.4 Torr).

Methyl 3-hydroxy-3-phenyl-2-vinylpropionate (1i). Bp 130-135°C (oven temperature)/10^{-2} Torr (Lit.[16] bp 100-110°C/10^{-4} Torr).

Preparation of Zn/2NaCl Sample for SEM, EDX and X-Ray Diffractometry. Method A. Sodium (7.5 mmol) was added to a suspension of anhydrous $ZnCl_2$ (3.75 mmol) in liquid ammonia (30 mL) at -78°C. After 15 min. at -33°C the ammonia was evaporated *nearly to dryness* and THF (30 mL) was added. The black slurry was refluxed for 45 min and then solvent was removed under vacuum.

Method B. Sodium (7.5 mmol) was added to $ZnCl_2$ (3.75 mmol) in mixture of liquid ammonia (5 mL) and THF (30 mL) at -78°C. After 15 min. at -33°C the ammonia was evaporated, resulting black slurry refluxed for 45 min and then THF was removed under vacuum. The samples (Zn/2NaCl) were stored under argon. For the investigations mentioned above each sample (grey powder) was quickly dispersed on an appropriate support and immediately placed into the sample chamber.

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