Organic Reactions in a Solid Matrix-VII[1]
Sodium on Alumina : A Convenient Reagent
for Reduction of Ketones, Esters and Oximes

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Abstract: Sodium dispersed on alumina is described and evaluated as a convenient off-the-shelf reagent (in a wax- coated form) for reduction of ketones , esters and oximes While isopropanol is the preferred proton donor for the reduction of ketones and oximes, t-butanol is the alcohol of choice for the reduction of esters

Reductions using alkali metals as electron source provide one of the important methods in organic synthesis. Although this method of reduction, which was among the first reductions of organic compounds, discovered some 130 years ago, has been overshadowed by more universal / convenient catalytic hydrogenations and metal hydride reductions for many classes of compounds, there remains a substantial group of dissolving metal reductions that are currently used synthetically because of advantages offered in chemo- or stereoselectivity. Usually, thermodynamically more stable alcohols are obtained from ketones, though exceptions have been noted[2]. Sodium metal alcohol reduction is a useful procedure for the reduction of ketones, esters and oximes[3]. However, it has the inconvenience of first having to prepare sodium powder, in order to effect an efficient conversion. In continuation of our earlier work[1,4] on reagents deposited in a solid matrix[5], we describe the preparation and evaluation of sodium-on-alumina, coated with paraffin, as a convenient off-the-shelf reagent for reduction of ketones, esters and oximes.

Sodium dispersed on alumina was first reported by Pines and Haag[6] in 1958 for the isomerization of monoolefins. In later years, it has been employed for the preparation of conjugated dienes[7], trienes[8], and terminal acetylenes[9]. Other reactions such as hydrogenations[10], dehydrogenations[11], polymerizations[12], condensation[13], and alkylation[14] have also been performed

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Table 1. Reduction of menthone with sodium-on-alumina and alcohols[a]

No.	Reagents			Reaction time (hr)	Recovery (%)	GC[b]					
	Sodium		Alcohol			Conversion (%)	Yield (%)	Product composition[c] (%)			
	Type of dispersion	g atom equiv.						Menthol (1)	Neomenthol (2)	Isomenthol (3)	Isoneomenthol (4)
1	Sodium sand	3	i-PrOH	4	86	100	86.0	69.0	1.7	22.0	5.1
2	Na-Al$_2$O$_3$	3	MeOH	5	85	46.5	39.5	73.7	3.2	15.2	7.7
3	"	3	i-PrOH	5	82	90	73.8	54.8	23.5	10.4	11.1
4	"	3	"	12	82	96	78.7	54.3	27.2	11.7	6.7
5	"	4	"	5	85	99	84.1	65.8	19.1	13.0	2.6
6	"	3	t-BuOH	5	85	62.7	53.3	75.9	1.4	18.9	3.6
7	"	3	"	12	80	79	63.2	76.0	2.7	20.3	0.9
8	"	4	"	5	85	79.8	67.8	75.1	2.5	17.8	4.5
Thermodynamic equilibrium[d]								60	26	13	1

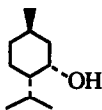(a) Reactions were carried out in refluxing tetrahydrofuran on a 10 mmole scale.
(b) Column : 12 ft, 10% diethylene glycol succinate on Chromosorb W (60-80 mesh); temp. 140^0; gas flow : 60 ml H$_2$ / min; RRT, neomenthol : neoisomenthol : menthol : isomenthol : : 1.00 : 1.13 : 1.27 : 1.50.
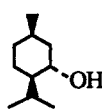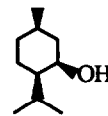(c) Corrected for 100% alcohol content
(d) Equilibrium temp. 210^{015}.
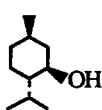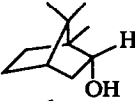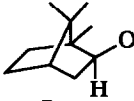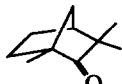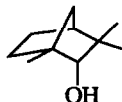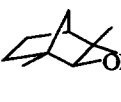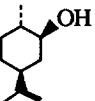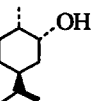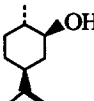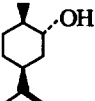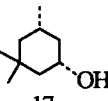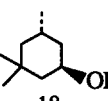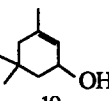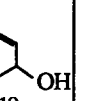
$\underline{1}$ $\underline{2}$ $\underline{3}$ $\underline{4}$

utilizing sodium supported on inert materials. However, it has not been evaluated for reductions. An important aim in carrying out the present investigation, besides evaluating sodium-on-alumina as a convenient reagent, was to study the stereochemical outcome in such reductions as compared to the usual traditional mode. It was anticipated that because of directional and aggregational constraints (e.g. approach of proton donor), the stereochemical outcome may be different.

Table 2. Reduction of various ketones with sodium-on-alumina and isopropanol[a]

No	Type of Sodium[b]	Reaction time (hr)	Recovery (%)	Conversion (%)	Yield (%)	GC Product composition[c] (%)			
Substrate :						..OH	▲OH		
1	Na	4	85	100	85	86	14		
2	Na-Al₂O₃	5	85	100	85	82	18		
Substrate : 5						6	7		
3	Na	4	89	86.5	77	87	13		
4	Na-Al₂O₃	5	85	72.0	61	74.5	25.5		
Substrate : 8						9	10		
5	Na	4	88	96	84	58.5	41.5		
6	Na-Al₂O₃	5	85	94	80	56.0	44.0		
Substrate : 11						12	13	14	15
7	Na	4	62	93	58	70	10	17	2
8	Na-Al₂O₃	4	59	96	57	59	21	18	2
Substrate : 16						17	18	19	
9	Na	4	60	65	39	79	3	18	
10	Na-Al₂O₃	8	62	60	37	72	11	16	

(a) Reactions were conducted in refluxing tetrahydrofuran on a 10 mmole scale; isopropanol was used as the alcohol.
(b) For each expt. sodium dust (3 g atom equivalent) or Na-Al₂O₃ (4 g atom equivalent of Na) per mole of the ketone was used.
(c) Corrected for 100% alcohol content.

Sodium-on-alumina containing 25% sodium metal was prepared and encapsulated in wax, as outlined in the Experimental part. This material, which is obtained as a grey-black free-flowing powder, has excellent shelf life, as there was no deterioration in its activity even after storage for 6 months at room temp. (~30[0]). For the reduction of ketones, it was found that an amount of this reagent equivalent to 4 g atoms of Na per mole of the substrate was essential for complete conversions. Table 1 summarises these results for menthone. Other ketones were next studied under these conditions and the results are depicted in Table 2. For purposes of comparison, reductions of each of these ketones were also performed by the usual sodium and alcohol reduction procedure[3b].

Though menthone used for reduction experiments was essentially free from isomenthone, the formation of four isomers of menthol from reductions (Table 1) is due to epimerization of menthone under the experimental conditions, for which there is sufficient prior precedence[16]. As anticipated[2], reductions of all the ketones investigated furnished the thermodynamically more stable alcohol as the main product (Tables 1, 2). However, a comparison of results of Na, isopropanol and Na-Al$_2$O$_3$, isopropanol reductions shows that in most cases, the Na-Al$_2$O$_3$, isopropanol reductions furnished relatively larger amounts of the unstable isomer. The mechanism currently accepted for Na / alcohol reductions is the one involving a ketyl radical anion[2]. However, the stereochemistry of such reductions has been a subject of much discussion and last reviewed by Pradhan[17], who proposed that the product stereochemistry is dictated by the structure of slightly pyramidalized ketyl radical anion; the direction of pyramidalization i.e. orbital extension is the result of FMO interactions[18]. The slight perturbation in the stereochemical outcome with Na-Al$_2$O$_3$, isopropanol reduction may be the result of some loss of preferred pyramidalization in the electron-rich Na-Al$_2$O$_3$ matrix. This appears to be supported by the fact that in the case of highly hindered ketone, fenchone (8), where pyramidalization is suppressed (or the energy barrier between the two

Table 3. Reduction of esters[a] and oximes[b] with Na-Al$_2$O$_3$ / alcohol[c].

No.	Substrate	Product	Isolated yield (%)
1	Methyl palmitate	Hexadacanol	70
2	Methyl oleate	9-Octadecenol	68
3	Ethyl benzoate	Benzyl alcohol	66
4	Ethylphenyl acetate	β-Phenylethyl alcohol	65
5	Cyclohexanone oxime	Cyclohexylamine	50
6	Cyclopentanone oxime	Cyclopentylamine	53
7	Benzaldehyde oxime	Benzylamine	60

[a] 6 g atom equivalent of Na per mole of ester; t-butanol as proton donor.
[b] 7 g atom equivalent of Na per mole of oxime; isopropanol as proton donor.
[c] Reactions were carried out on 5 mmole scale

pyramidal ketyl radical anions is reduced)[19, 20] the two reagents furnish essentially identical products (Table 2, entries 5, 6).

Esters and oximes

Na-Al$_2$O$_3$, alcohol reduction was next extended to a few esters and oximes. These reductions were best carried out in refluxing toluene and to avoid excessive loss of sodium, t-butanol instead of isopropanol was found to be the preferred alcohol. Conversions were 100%, and the isolated yields of alcohols (65-70%) and amines (50-60%) were in the range recorded in the literature for Na-alcohol reductions[21]. Relevant data are given in Table 3.

EXPERIMENTAL

The following instruments were used for spectral / analytical data : Perkin-Elmer infrared spectrometer, model 267; Perkin-Elmer model R 32 (90 MHz) NMR spectrometer; Hewlett-Packard 5712 and 7624 A gas chromatographs. For gas chromatography (analytical), ss columns (360 cm x 0.6mm) packed with 10% SE 30 or 10% Carbowax 20 M or 10% diethyleneglycol polysuccinate on Chromosorb W (60-80 mesh) were employed; while for preparative GC, 360 cm x 1.0 cm ss column, packed with 20%Carbowax 20 M on 60-80 mesh Chromosorb W was used.

All compounds described in this communication are known and after recovery from reaction mixtures were separated by preparative GC and the product recognised by IR and PMR.

Alumina (-80, +200 mesh) was obtained from CAP Bareilly and was activated at 490-500^0 for 12 hr under N$_2$. It was allowed to cool under N$_2$ and then bottled.

All substrates were either available in the laboratory or were prepared using known standard procedures.

Preparation of Sodium-on-alumina

A flame dried assembly consisting of a 500 ml RB flask equipped with an efficient hershberg-type stirrer, a condenser, a thermometer well, and a N$_2$ inlet was charged with 37.5 g of alumina and activated at 220±10^0, and 12.5 g of clean Na metal pieces were added (10 min). The temp. was maintained at ~ 165^0 and the mixture stirred vigorously for 2 hours when a grey-black, free-flowing powder resulted. The temperature was next lowered to ~ 100^0 and 6.25 g molten paraffin wax (m.p. 50-60^0) was added and the mixture stirred vigorously at this temp. for 2 hrs. The material was next allowed to cool to room temperature and the free-flowing black powder was stored in a wide-mouth bottle. The product weighed 54-56 g.

The above product was estimated for sodium, by reacting a sample with methanol and quantitatively estimating evolved hydrogen. A typical preparation had ~ 21% active Na.

Reduction of ketones

The following reduction of menthone to menthols is illustrative of the general procedure.

Na-Al$_2$O$_3$ (21% active Na; 4.5 g ~ 0.04 g atom Na) was placed in a dry 3-neck 50 ml RB flask, rapidly washed with dry hexane (10 ml x 6) and then with THF (10 ml x 2) and finally covered with THF (30 ml). The flask was next assembled in an assembly having a stirrer, reflux condenser, N$_2$ inlet and a pressure-equilibrating addition funnel. A mixture of menthone (1.54 g, 0.01 mole) and isopropanol (2.4 g, 0.04 mole) was added (5-10 min) to Na-Al$_2$O$_3$ with stirring. The reaction mixture was stirred and refluxed for 5 hr and then cooled to ~ 0^0 and treated with ice water (5 ml). The slurry was filtered and alumina washed with ether (20 ml). The combined filtrate and washings were further diluted with ether (40 ml) and washed with brine (15 ml x 3) and dried (Na$_2$SO$_4$). Removal of solvent furnished 1.32 g of product, which after distillation was analysed by GC.

Reduction of esters

The Following procedure is typical :

Na-Al$_2$O$_3$ (21% active Na; 3.3 g ~ 0.03 g. atom Na) was freed of wax, as above, and covered with dry toluene (50 ml). A mixture of ethyl palmitate (1.42 g, 0.005 mole) and t-butanol (2.22 g, 0.03 mole) was slowly introduced (5-10 min) with stirring. The reaction mixture was additionally stirred and refluxed for 5-6 hr for completion of the reduction. Usual work-up afforded 0.84 g of 1-hexadecanol after distillation.

Reduction of oximes

Reduction of oximes was carried out with 7 g atom equivalents of Na-Al$_2$O$_3$ and isopropanol (7 mole equiv.) in refluxing toluene for 3-4 hr as above. After the reaction was complete (TLC monitoring) the reaction mixture was cooled to ~ 0^0 and quenched with ice water (5 ml) and alumina removed by filtration. The filtrate was acidified with HCl aq. (1:1) to pH 2-3 and mixture of water and toluene stripped off by distillation from a water-bath under reduced pressure. The residual solid was treated with 40% KOH aq. and the amine taken up in ether (15 ml x 6). Usual work-up furnished the required amine, which was purified by distillation.

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