Reduction of Nitrosoamides to Alcohols Using Sodium Borohydride

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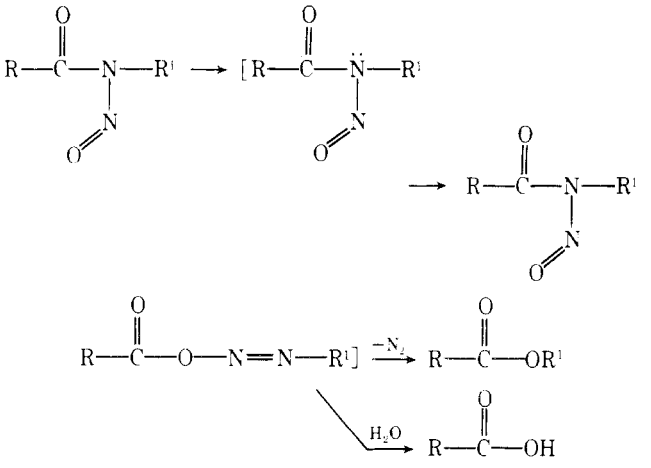
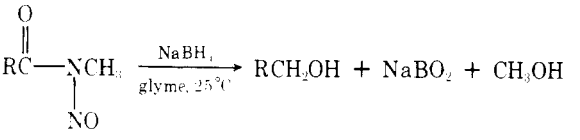
Carboxylic acids, esters, and amides are generally resistant to reduction with sodium borohydride.[1] This alkali metal borohydride reduces carboxylic acids to alcohols only after converting them to the corresponding acid chloride in an inert solvent.[2] Esters with very electronegative alcohol moieties can also be reduced to primary alcohols.[3] Electron withdrawing groups α to the carbonyl group facilitate the reduction of carboxylic acids by sodium borohydride. Amides are not likely to be reduced to primary alcohols by borohydrides. However, one case has been reported in which *N*-tosylpyroglutamic acid amide underwent ring cleavage to the primary alcohol[4] with lithium borohydride. The introduction of a strongly electronegative group on the amide nitrogen causes the compound to behave in this case as an acid chloride. Another good example of this behavior is observed in the rapid solvolysis of nitrosoamides to the corresponding ester through an alkyl diazotate intermediate,[5,6] as in Scheme I. The formation of this intermediate might explain why nitrosoamides are direct acting mutagens.[7,8]

Most of our basic knowledge of the chemistry of nitrosoamides follows from the pioneering work of White[6] and Huisgen et al.[5] Their work dealt primarily with the introduction of the nitroso group, the isomerization of nitrosoamides to the diazo esters, and the practical application of these to deamination chemistry.[9] Other practical applications to organic synthesis of the chemical reactivity of nitrosoamides have not been thoroughly explored. This paper reports conversion under mild conditions and with good yields of nitrosoamides to primary alcohols using sodium borohydride.

Scheme I



Scheme II



The nitrosoamides were prepared by previously described methods.[5,7,10] Reductions were carried out in dry glyme at room temperature for 2–8 h; the yields of primary alcohols ranged from 50 to 82%, Scheme II. The corresponding primary alcohol is also formed by the reduction of the nitrosoamides in water with sodium borohydride. This method is not practical since the reduction step competes with the formation of an alkyl diazotate and subsequent formation of the carboxylic ester. Parallel experiments carried out with the methyl ester

Table I. Reduction of *N*-Methyl-*N*-nitrosoamides in Glyme at 25 °C

compd	registry no.	$NaBH_4$,[a] mol equiv	time, h	product	registry no.	yield, %	bp or mp, °C	lit. value[11]
$PhCON(NO)CH_3$	63412-06-6	1.2	2	$PhCH_2OH$	100-51-76	84	*b*	bp_{760} 205
$PhCON(NO)CH_3$		0.5	3	$PhCH_2OH$		60	*b*	bp_{760} 205
$PhCH_2CONNOCH_3$	68782-25-2	1	1	$PhCH_2CH_2OH$	60-12-8	71	bp_{15} 108–10	bp_{10} 99–100
$CH_3(CH_2)_2CON(NO)CH_3$	16395-81-6	1	3	$CH_3(CH_2)_3OH$	71-36-3	50	*b*	bp_{760} 117.5
$CH_3(CH_2)_{12}CON(NO)CH_3$	16514-82-2	1	3	$CH_3(CH_2)_{13}OH$	112-72-1	78	mp 35–7	mp 39–40
$CH_3(CH_2)_{12}CON(NO)CH_3$		1.2	8	$CH_3(CH_2)_{13}OH$		79	34–6	mp 39–40
$CH_3(CH_2)_{10}CON(NO)CH_3$	16395-85-0	1	3	$CH_3(CH_2)_{11}OH$	112-53-8	41	bp_{20} 138–40	mp 26
$CH_3(CH_2)_{10}CON(NO)CH_3$		1.2	8	$CH_3(CH_2)_{11}OH$		65	bp_{20} 138–40	mp 26
$CH_3(CH_2)_8CON(NO)CH_3$	16395-84-9	1	2.5	$CH_3(CH_2)_9OH$	112-30-1	54	bp_{20} 115	bp_{760} 229
$CH_3(CH_2)_8CON(NO)CH_3$		1.2	8	$CH_3(CH_2)_9OH$		63	bp_{20} 115	bp_{760} 229

[a] Sodium borohydride was added at 0 °C. [b] The purity of the undistilled product was determined by GLC analysis.

Table II. Physical and Spectral Properties of *N*-Methyl-*N*-nitrosoamides

compd	mp or bp (lit.), °C	method of preparation	NMR ($CDCl_3$), δ	IR, cm^{-1}
$PhCON(NO)CH_3$	nondistillable liquid	ref 5	3.36 (s, 3 H), 7.60–7.88 (m, 5 H)	1710, 1600
$PhCH_2CON(NO)CH_3$	mp 40–2 (40)	ref 10	3.13 (s, 3 H), 3.52 (s, 2 H), 7.36 (s, 5 H)	3030, 1735, 1600
$CH_3(CH_2)_2CON(NO)CH_3$	bp 70–3 (20 mmHg) (59–60 ° at (14 mmHg)	ref 5	1.06 (t, 3 H), 1.84 (q, 2 H), 3.12 (s, 3 H), 3.16 (t, 2 H)	2920, 1730, 1500
$CH_3(CH_2)_{12}CON(NO)CH_3$	mp 41–3 (43–5)	ref 7	0.87 (t, 3 H), 1.24 (s, 20 H), 1.8 (m, 2 H), 3.11 (t, 2 H), 3.17 (t, 2 H)	2915, 1725, 1510, 1420 ($CHCl_3$)
$CH_3(CH_2)_{10}CON(NO)CH_3$	mp 34–6 (34–5)	ref 7	0.89 (t, 3 H), 1.28 (s, 16 H), 1.8 (m, 2 H), 3.13 (s, 3 H), 3.18 (t, 2 H)	2920, 1725, 1500, 1465
$CH_3(CH_2)_8CON(NO)CH_3$	mp 20–3 (21.5–22.5)	ref 7	0.90 (t, 3 H), 1.28 (b, 12 H), 1.80 (t, 2 H), 3.13 (s, 3 H), 3.19 (t, 2 H)	2920, 1729, 1500, 1460

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verified the fact that common esters are not reduced by sodium borohydride.[1] The reduction of *N*-methyl-*N*-nitrosobenzamide at 5 °C in water with 1 equiv of sodium borohydride for 1 h gave a yield of 76% benzyl alcohol and 7% methyl benzoate. The reaction in water is much faster than in glyme, but the use of a nonprotic solvent appears to decrease considerably the possibility of ester formation.

At this point the reduction mechanism remains unclear. The metal borohydride may add directly to the carbonyl function of the nitrosoamide, or epimerization of the nitrosoamide to the diazotate (Scheme I) may take place first followed by the reduction of this intermediate before it can decompose to the ester. Since the diazotate is a short-lived intermediate,[6] it seems likely that this reaction follows a mechanism similar to the reduction of acid chlorides, that is, direct addition of borohydride to the carbonyl function.[2]

Warning. Many nitrosoamides are mutagenic without liver activation. These compounds should be considered contact carcinogens and must be handled with great caution.

Experimental Section

Proton magnetic resonance spectra were taken on a Varian XL-100 Spectrometer using $CDCl_3$ as the solvent, with 0.5% tetramethylsilane as the internal standard. The IR spectra were obtained on a Perkin-Elmer 467 spectrometer. Melting points were determined in an Electrothermal capillary melting point apparatus. Purity determinations by gas–liquid chromatography (GLC) were carried out in a Shimadzu Model 4BM chromatograph equipped with a Hewlett-Packard 18652A A/D converter coupled to the recorder of a flame ionization detector. An 8 ft 8% H1-EFF-1BP coated on a Gas-Chromosorb Q column was used (Applied Science Laboratories Inc., State College, Pa.). The acid chlorides used to prepare the amides were obtained from Aldrich Chemical Co., Milwaukee, Wis.

Preparation of Methylamides. *N*-Methylbenzamide, mp 78–80 °C (lit.[12] mp 80 °C); *N*-methyl-2-phenylacetamide, mp 56–7 °C (lit.[13] mp 58 °C); *N*-methylbutyramide, bp 110–11 °C (15 mmHg) (lit.[14] bp 156 °C (90 mmHg)); *N*-methylmyristoylamide, mp 76–8 °C (lit.[14] mp 78.4 °C); *N*-methyldodecanoyl amide, mp 68 °C (lit.[14] mp 67–9 °C); and *N*-methyldecanoylamide, mp 57–8 °C (lit.[14] mp 57.3 °C) were prepared by dissolving methylamine hydrochloride in 5% aqueous sodium hydroxide solution followed by addition of the acid chloride.

Preparation of Nitrosoamides. These compounds were prepared from the corresponding amides by published methods, see Table II.

Reduction of *N*-Methylnitrosoamides with $NaBH_4$. A typical reduction procedure was as follows: A 0.5 M solution of nitrosoamide in glyme was cooled to 0 °C in a salt–ice water bath and sodium borohydride was added in small lots over a period of 5 to 10 min. Once the addition was complete, the cooling bath was removed and the mixture stirred at room temperature for 2–8 h. The reaction mixture was cooled to 5 °C and ice chips were added. Excess sodium borohydride was decomposed with 10% hydrochloric acid. The solution was extracted with dichloromethane, washed with 5% sodium bicarbonate solution, dried over sodium sulfate, and filtered through a pad of magnesium sulfate and the solvent was removed on a rotary evaporator. The crude product was distilled and/or analyzed by GLC; 1-tetradecanol was recrystallized from aqueous ethanol. All products were compared and found to be identical with authentic samples of the primary alcohols. Reaction times and product yields are given in Table I.

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Registry No.—*N*-Methylbenzamide, 613-93-4; *N*-methyl-2-phenylacetamide, 6830-82-6; *N*-methylbutyramide, 17794-44-4; *N*-methylmyristoylamide, 7438-09-7; *N*-methyldodecanoylamide, 27563-67-3; *N*-methyldecanoylamide, 23220-25-9; methylamine hydrochloride, 593-51-1; benzoyl chloride, 98-88-4; benzeneacetyl chloride, 103-80-0; butanoyl chloride, 141-75-3; myristoyl chloride, 112-64-1; dodecanoyl chloride, 112-16-3; decanoyl chloride, 112-13-0; sodium borohydride, 16940-66-2.

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Dienic Reactivity of 3,5-Cycloheptadien-1-one

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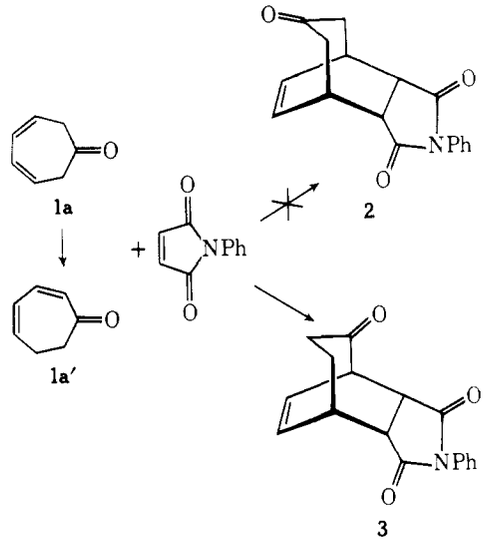
The reaction of 3,5-cycloheptadienone (**1a**) with *N*-phenylmaleimide was shown[2,3] to afford the Diels–Alder adduct **3** rather than the expected adduct **2** (eq 1). Presumably the



(1)

dienic reactivity of cycloheptadienone **1** is low and under the reaction conditions the 3,5-isomer **1a** is transformed via enolization into the 2,4-isomer **1a**, leading subsequently to the adduct **3**.[4] This lack of dienic reactivity of the 3,5-isomer **1a** and the anomalously short wavelength absorption (λ_{max} 217 nm) have been attributed to a nonplanar diene moiety as its most stable conformation. Indeed, molecular models indicate considerable strain for the planar conformation of the diene.

Consequently, it came to us as some surprise when the singlet oxygenation of **1a** gave the apparently unfavorable 3,5-type Diels–Alder adduct instead of the expected ene-type reaction.[5] In view of this unusual result, we decided to examine the dienic reactivity of 3,5-cycloheptadienones **1a–d** with potent dienophiles such as 4-phenyl-1,2,4-triazolin-3,5-dione. In all cases the Diels–Alder adduct **4** of the 3,5-isomers **1** was formed in high yield. The results are summarized in Table I and exhibited in Scheme I. Structure proof of the adducts **4**

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