Improved Reduction of Nitrimines to Nitramines Using Sodium Borohydride and Acetic Acid

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Imines can generally be reduced efficiently with sodium borohydride, lithium aluminum hydride, catalytic hydrogenation, or dissolving metal reductions. However, in the presence of many functional groups (e.g., esters, ketones, nitro groups, and double bonds), these methods often cannot be employed for imine reduction due to concomitant reduction of the functional group.[1] In such cases, sodium borohydride is usually the reagent of choice,[2] but even it will not always reduce nitro-substituted imines in good yield.

The present study provides a significant improvement in the reduction of nitrimines to nitramines by the addition of acid to the reaction mixture (Table I). The procedure is simple and general, yet provides greatly improved yields over the usual sodium borohydride reduction procedures. When 3β-acetoxy-5α-chloro-6-nitriminocholestane (1) was treated with sodium borohydride in dioxane and ethanol, the nitramine 2 was obtained in only 15% yield regardless of reaction time; no nitrimine was recovered. Addition of glacial acetic acid to the reaction mixture dramatically increased the yield of recrystallized product to 76%. Similarly, sodium borohydride reduction of 3-chloro-3-methyl-2-nitriminobutane (3) without acid gave only a trace of the nitramine 4, but when the reduction was run in the presence of acetic acid, the yield of nitramine again jumped to 76%. Although a mechanistic study of the role of acetic acid was not undertaken, the presumed reducing agent is an acyloxyborohydride species formed by the initial reaction of acetic acid and sodium borohydride. Sodium triacetoxyborohydride is known to reduce aldehydes under mild conditions.[3]

That this reduction is general for a variety of structurally different nitrimines and can be accomplished without concomitant reduction of the nitro moiety is illustrated by the reduction of 1-nitrimino-9-chloro-10-methyldecalin (5) and 1-chloro-1-(α-nitriminoethyl)cyclohexane (7) to their corresponding nitramines 6 and 8, respectively, in good yield.

Sodium borohydride has been used in acidic media to reduce aldehydes,[3] oxazines,[4] and indoles.[5] These examples generally require the reaction medium itself to be acidic, whereas in the present study only a relatively small amount of acetic acid is required, not enough to acidify the reaction mixture.

Experimental Section

All melting points were uncorrected. NMR spectra were recorded on a Varian A-60 spectrometer using Me_4Si as an internal standard. Infrared spectra were recorded on a Perkin Elmer 137 spectrometer.

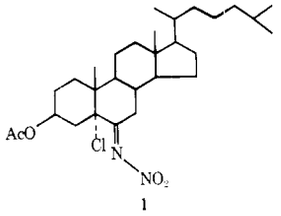
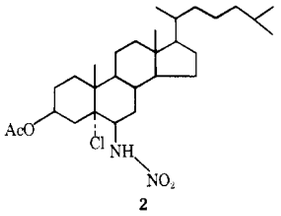
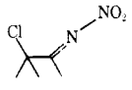
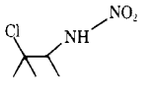
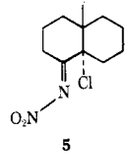
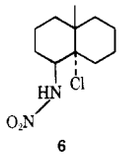
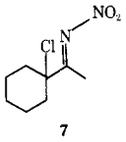
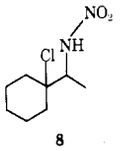
General Procedure for Nitramine Reduction. a solution of 23.2 mmol of nitrimine in 165 mL of dioxane, 165 mL of ethanol, and 0.5 mL of glacial acetic acid was stirred at 0 °C while 229 mmol of sodium borohydride was added as fast as possible while still controlling frothing. The mixture was stirred for 30 min at 0 °C, and 1.5 mL of glacial acetic acid was added (total of 35.0 mmol of HOAc). After stirring for 1 h at 0 °C followed by 1 h at room temperature, the mixture was diluted with 700 mL of 3% aqueous acetic acid and extracted with methylene chloride. The extracts were washed with water, dried, and concentrated in vacuo to give the crude nitramine which was either recrystallized or distilled.

3β-Acetoxy-5α-chloro-6β-nitraminocholestane (2). Sodium borohydride reduction as above of 1[6] gave a white solid which was recrystallized from acetone to give a 76% yield of **2**: mp 206–206.5 °C (dec); IR (Nujol) 5.85 (s) and 6.20 (s) μm; NMR ($(CD_3)_2SO$) δ 5.50–4.90 (m, 1 H, –COOCH<), 2.28–0.72 (m, 30 H, aliphatic), 1.99 (s, 3 H, CH_3CO–), 1.19 (s, 3 H, C-19 methyl), 0.90 (br s, 6 H, C-26 and C-27 methyls), 0.80 (br s, 3 H, C-21 methyl), and 0.69 (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{49}N_2O_4Cl$: C, 66.32; H, 9.50; N, 5.33; Cl, 6.75. Found: C, 66.40; H, 9.29; N, 5.16; Cl, 6.83.

3-Chloro-3-methyl-2-nitriminobutane (3). A solution of 200 g (2.85 mol) of 2-methyl-2-butene in 1200 mL of methylene chloride was stirred at 0 °C while nitrosyl chloride was slowly bubbled into the solution for 1.3 h. The resultant blue solution was stirred for 1.5 h at 0 °C and concentrated in vacuo without heating to give ca. 200 g of 3-chloro-3-methyl-2-butanone oxime as an oily blue-green solid. Further purification was not attempted.

Table I. Reduction of Nitrimines with Sodium Borohydride and Acetic Acid[a]

Nitrimine	Nitramine	Yield, %	mp or bp, °C
 1	 2	76	mp 206 (dec)
 3	 4	76	bp 60/0.15 mm
 5	 6	70	mp 126–127
 7	 8	41	mp 84–85

[a] Registry numbers: 1, 31239-36-8; 2, 63215-89-4; 3, 63215-90-7; 4, 63215-91-8; 5, 63215-92-9; 6, 63215-93-0; 7, 28042-44-6; 8, 28042-46-8.

The 200 g of 3-chloro-3-methyl-2-butanone oxime in 1600 mL of methylene chloride was stirred at 0 °C while nitrosyl fluoride was slowly bubbled into the solution for 1.25 h. The green solution was stirred at 0 °C for 3.5 h, followed by 1.5 h at room temperature. The mixture was slowly poured into saturated aqueous sodium carbonate and washed with saturated aqueous sodium carbonate, water, and brine. The organic layer was dried, filtered, and concentrated in vacuo to give a blue oil which was distilled giving 21.00 g (0.128 mol, 4% overall) of 3-chloro-3-methyl-2-nitriminobutane: bp 48–50 °C/0.5 mm; IR (neat) 6.17, 6.36 (s) and 6.92 μm; NMR ($CDCl_3$) δ 2.24 (s, 3 H, $-(CH_3)C{=}N-$) and 1.83 (s, 6 H, $-((CH_3)_2)CCl$).

Anal. Calcd. for $C_5H_9N_2O_2Cl$: C, 36.49; H, 5.51; N, 17.02; Cl, 21.54. Found: C, 36.30; H, 5.59; N, 17.27; Cl, 21.51.

3-Chloro-3-methyl-2-nitraminobutane (4). Sodium borohydride reduction as above of **3** gave a yellow liquid which was distilled giving a 76% yield of **4** as colorless liquid: bp 60 °C/0.1 mm; IR ($CHCl_3$) 6.35 and 6.88 μm; NMR ($CDCl_3$) δ 8.55 (br m, 1 H, >NH), 4.44 (br q, 1 H, J = 6.5 Hz, $>CH-NHNO_2$), 1.67 (s, 3 H, $>(CH_3)CCl$), 1.64 (s, 3 H, $>(CH_3)CCl$), and 1.39 (d, 3 H, J = 6.5 Hz, $>(CH_3)CNH-$).

Anal. Calcd for $C_5H_{11}N_2O_2Cl$: C, 36.05; H, 6.66; N, 16.81; Cl, 21.28. Found: C, 36.09; H, 6.52; N, 16.28; Cl, 21.49.

1-Oximino-9-chloro-10-methyldecalin and 1-Nitrimino-9-chloro-10-methyldecalin (5). A solution of 58.0 g (0.387 mol) of 10-methyl-$\delta^{1,9}$-octalin[7,8] in 1 L of methylene chloride at 0 °C was stirred while nitrosyl chloride was slowly bubbled in for 20 min. The reddish-brown solution was stirred at 0 °C for 3 h and concentrated in vacuo to give a light-green solid which was washed with cold hexane and filtered giving 22.73 g (0.105 mol, 27%) of 1-oximino-9-chloro-10-methyldecalin, mp 128–132 °C (dec). The filtrate was concentrated in vacuo to give a dark oil which was chromatographed on a 6.5 × 34.5 cm column of silicic acid (Mallinckrodt, Silic Ar, CC-7) slurry packed in 10% chloroform in hexane. Elution in 500-mL fractions gave fraction 1, 1.38 g of unidentified oil, and fractions 2–4, 25.05 g (0.102 mol, 26%) of **5**: NMR ($CDCl_3$) δ 3.30–1.00 (m, 14 H, aliphatic) and 1.11 (s, 3 H, methyl); IR ($CHCl_3$) 6.19, 6.38, and 6.90 μm.

Anal. Calcd for $C_{11}H_{17}N_2O_2Cl$: C. 53.99; H, 7.00; N, 11.45. Found: C, 54.22; H, 7.16; N, 11.11.

1-Nitrimino-9-chloro-10-methyldecalin (5). A solution of 22.73 g (0.105 mol) of 1-oximino-9-chloro-10-methyldecalin in 1.5 L of methylene chloride at 0 °C was stirred while nitrosyl chloride was slowly bubbled in for 30 min. The reddish-brown solution was stirred at 0 °C for 5.5 h, poured into water, washed with water and brine, dried, filtered, and concentrated in vacuo to give a yellow oil which was chromatographed on a 3.5 × 39.5 cm column of silicic acid (Mallinckrodt, Silic AR, CC-7) slurry packed in 10% chloroform in hexane. Elution in 200-mL fractions gave fraction 1, nil, fractions 2–5, 14.49 g (0.059 mol, 56%) of **5**, and fraction 6, 160 mg.

A small sample of **5** was recrystallized from ethanol, yielding white crystals which melted at 61–62 °C.

1-Nitramino-9-chloro-10-methyldecalin (6). Sodium borohydride reduction as above of **5** gave a white solid which was washed with hexane, filtered, and vacuum dried giving a 70% yield of **6** as a white solid: mp 136 °C (dec); NMR ($CDCl_3$) δ 9.10–8.50 (br m, 1 H >NH), 4.76–4.49 (br m, 1 H, $>CH-NHNO_2$), 2.68–0.84 (m, 14 H, aliphatic), and 1.20 (s, 3 H, methyl); IR ($CHCl_3$) 6.24, 6.38, 6.74, and 6.84 μm.

Anal. Calcd for $C_{11}H_{19}N_2O_2Cl$: C, 53.55; H, 7.76; N, 11.35; Cl, 12.97. Found: C, 53.52; H, 7.62; N, 11.30; Cl, 12.99.

1-Chloro-1-(α-nitraminoethyl)cyclohexane (8). Sodium borohydride reduction as above of **7**[1] gave a yellow oil which crystallized from hexane. Recrystallization from hexane afforded a 41% yield of **8** as a white solid: mp 84–85 °C (lit.[1] mp 91–92.5 °C). Both NMR and IR were in agreement with reported spectra.[1]

Registry No.—Acetic acid, 64-19-7; sodium borohydride, 16940-66-2; 2-methyl-2-butene, 513-35-9; nitrosyl chloride, 2696-92-6; 3-chloro-3-methyl-2-butanone oxime, 3238-16-2; 10-methyl-$\Delta^{1,9}$-octalin, 13942-77-6; 1-oximino-9-chloro-10-methyletacalin, 63215-94-1.

References and Notes

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Total Synthesis of (±)-Damsin

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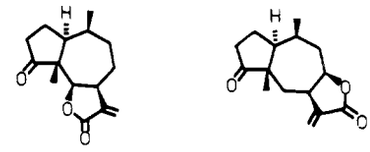
Among the many isolated sesquiterpene lactones[2a] the nonisoprenoid hydroazulenic pseudoguaianolides[2b] represent the largest family. Several synthetic approaches[3–5] to these compounds have appeared, recently culminating in the total syntheses of (±)-damsin[6] (**1**) and (±)-confertin[7] (**2**). In this



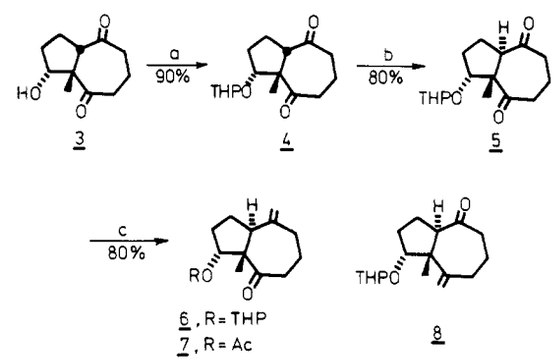
1 **2**

paper we report an independent synthesis of (±)-damsin and describe some transformations of synthon **3** which could be of value for the synthesis of other pseudoguaianolides.

Our synthetic plan centers about the hydroazulenic dione **3**, which we prepared via oxidative cleavage of a tricyclo[5.3.0.$0^{6,10}$]decanetriol.[5,8] This intermediate seems ideally suited for further transformation to pseudoguaianolides. The necessary trans ring fusion of the natural representatives is favored in an equilibrium isomerization process.[9] The two carbonyl functions are expected to be easily differentiated due to a marked difference in steric environment. The hydroxyl group allows for further functionalization of the cyclopentane ring; its α-orientation could, however, disturb the exercise of the stereochemical control by the angular methyl group.[4,10]

The isomerization of compound **4** could easily be achieved in alkaline medium (Scheme I). The equilibrium (85% trans, 15% cis) is largely in favor of the trans ring-fused product, which can be separated from the contaminating dione **4** by crystallization. The presence of a cis-fused γ-butyrolactone in many pseudoguaianolides, e.g., in damsin (**1**), demands alkylation in the 5 position after protection or transformation of the 2-carbonyl function. It has been suggested[4] that the alkylation of similar trans-fused hydroazulenic ketones with methyl bromoacetate proceeds poorly, unless one or more additional trigonal centers are present in the enolate, thereby lowering the steric congestion of the seven-membered ring. These considerations coupled with the anticipated formation of a β-methyl group on catalytic hydrogenation of an *exo*-methylene function led us to synthesize ketone **6**. Under the

Scheme I[a]



3 **4** **5**

6, R = THP
7, R = Ac

8

[a] a, DHP, *p*-TsOH; b, NaOH, MeOH; c, $(C_6H_5)_3P{=}CH_2$, THF.