N,N-Dideuterated Alkylamines from *N*-Benzylidenealkylamines. Improved Lithium/Ethylamine Reduction of α,β-Unsaturated Ketones

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As commonly performed, the lithium/liquid ammonia or lithium/alkylamine reduction of α,β-unsaturated ketones is often attended by appreciable overreduction to monomeric secondary alcohols, formation of dimeric products, and/or enolization leading to recovery of starting material[1]. Consequently, the synthesis of saturated ketones by this method as well as the preparation of β-deuterated ketones by use of lithium in ammonia-d_3 or in an *N,N*-dideuterated alkylamine, even though these are procedures of choice[2], frequently give only modest yields of desired products. Here we report a new, efficient route to ethylamine-*N*d_2 and *n*-propylamine-*N*d_2, together with significantly improved conditions for the lithium/ethylamine reduction of α,β-unsaturated ketones.

Although direct exchange with D_2O is ideally suited for the *N*-deuteration of water-insoluble amines (cf. Ref.[2], p. 15), it is inconvenient for occasional laboratory preparation of low-molecular weight, water-soluble *N*-deuterated alkylamines. An alternative method involves deuterolysis of tetraarsenic hexakis[alkylimides][3], but the synthesis and handling of such starting materials are more complicated than in the present procedure based on the deuterolysis of the easily prepared *N*-benzylidene derivative of the amine (Scheme **A**).

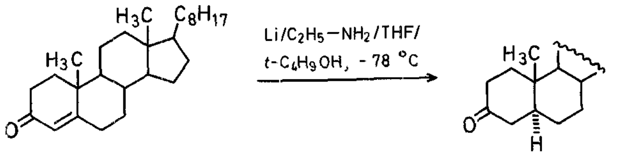
$$C_2H_5{-}NH_2 + C_6H_5{-}CH{=}O \xrightarrow[-H_2O]{} C_6H_5{-}CH{=}N{-}C_2H_5$$

$$\xrightarrow[-\,C_6H_5{-}CH{=}O]{BF_3\cdot O(C_2H_5)_2/D_2O} C_2H_5{-}\overset{\oplus}{N}D_3\ X^{\ominus} \xrightarrow{K_2CO_3} C_2H_5{-}ND_2$$

Scheme **A**

Boron trifluoride etherate added to D_2O provides a convenient, inexpensive source of acid for the deuterolysis of the Schiff base. After removal of the benzaldehyde by extraction with cyclohexane, an excess of potassium carbonate is added to liberate the deuterated amine from its salt. The amine is collected by distillation and freed of D_2O by redistillation from lithium metal. In this manner, ethylamine-*N*d_2 and *n*-propylamine-*N*d_2 of high isotopic purity are produced in 56% and 71% yield, respectively, from the corresponding *N*-benzylidene derivative.

In our hands reduction of cholest-4-en-3-one (**1**) with lithium in refluxing propylamine in the absence of an added proton source as recommended by Fétizon and Gore[4] gave only poor yields (<30%) of 5α-cholestan-3-one (**2**). We therefore explored other conditions for this reduction before undertaking the preparation of 5α-deuteriocholestan-3-one[5] required for the synthesis of isotopically pure 5α-deuteriocholesta-1,3-diene[6]. To our surprise, we found that superior results are obtained when the reduction is conducted not at the boiling point of the amine but at Dry Ice temperature (−78 °C) with a substantial excess of lithium in ethylamine in the presence of *t*-butanol as a proton source. Under these conditions, **1** is converted into **2** in 92% yield without detectable formation of cholestanol or recovery of cholestenone (Scheme **B**).



1 **2**

Scheme **B**

By use of ethylamine-*N*d_2 in the presence of *t*-butanol-*O*d, 5α-deuteriocholestan-3-one is obtained in comparable yield. After removal of deuterium at C-2 and C-4 by proton exchange (CH_3OH/CH_3ONa), the mass spectrum shows this product to be at least 98% isotopically pure monodeuterated cholestanone[7].

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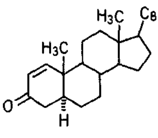
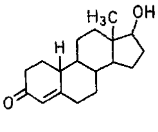
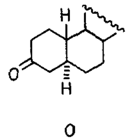
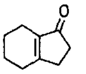
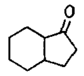
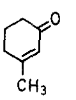
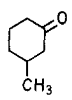
Table. Lithium/Ethylamine/*t*-Butanol Reductions of Enones at −78 °C

Enone	Product	Reaction scale	Yield[a] [%]	m.p. or b.p./torr [°C] found	m.p. or b.p./torr [°C] reported
1 	**2**	1.4 mmol	92	130–131.5°	129–130°[10]
	2	0.2 mmol	89	130–131°	
		1.5 mmol	88	130–131°	130–132°[11]
		15 mmol	64 (87)[b,c]	103–107°/20	81.5–86.5°/10[12]
		30 mmol	54 (97)[b]	85–89°/50	64–65°/30[13]

[a] Yield of crystallized or distilled product.

[b] Yield by G.L.C. (conditions: 6′×0.25″ column of 10% OV-17 on 100–120 mesh Gas Chrom Q); lower yield isolated due primarily to mechanical losses.

[c] Mixture of *cis-trans* isomers.

The general utility of this low-temperature reduction procedure is illustrated in the Table. In each case the saturated ketone is produced in good yield without detectable recovery of starting material or formation of monomeric secondary alcohol. Significantly, without the added alcohol proton source the reaction is exceedingly slow, and considerable amounts of starting enone are recovered. Under the same low-temperature conditions, use of excess lithium and *t*-butanol in liquid ammonia gives the secondary alcohol as well as recovered enone.

Ethylamine-*Nd*$_2$:

To a dry, argon-flushed, 500-ml Erlenmeyer flask provided with a septum inlet and a magnetic stirring bar are added *N*-benzylideneethylamine[8] (91.5 g, 0.688 mol) and deuterium oxide (99.8%, Stohler, 68 ml, 3.75 mol). With vigorous stirring, freshly distilled boron trifluoride etherate (97 g, 0.68 mol) is introduced over a period of 10 min with evolution of heat. Stirring is continued for 4 h without cooling, and cyclohexane (75 ml) is added. The resulting two phases are allowed to separate, and the upper layer is removed by positive-pressure (argon) cannula transfer. Extraction with additional cyclohexane (50-ml portions) is repeated twice. The lower acidic layer is then transferred by cannula to a 500-ml three-neck, round-bottom flask immersed in an oil bath and equipped with a stout Tru-Bore stirrer, an argon-flushed equilibrated addition funnel fitted with an 8-mm bore stopcock, and a gas adapter connected sequentially by Tygon tubing to two cold traps cooled in Dry Ice/acetone. With moderate stirring, anhydrous potassium carbonate (~250 g, previously dried at 220 °C) is slowly and cautiously added *(initial foaming)* from the addition funnel as the amine (wet with D_2O and initially containing some CO_2) distils into the traps. When enough carbonate has been added to produce a stiff, granular paste, the remaining amine is collected by gentle heating (60–80 °C). The condensed amine is transferred by cannula from the cold traps (frozen D_2O remains behind) to a dry, argon-flushed, septum-stoppered, 50-ml round-bottom flask containing a magnetic stirring bar and lithium shot[9] (200 mg). After stirring for 1 h (blue color develops), the dried product is distilled through a cannula into a receiver cooled in Dry Ice to give anhydrous ethylamine-*Nd*$_2$; yield: 18 g (56%); b.p. 16–17 °C/750 torr.

I.R. (CCl_4): ν=2950; 2110; 1455; 1375; 1195; 960 cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ=2.65 (q, 2H, J=7.5 Hz); 1.21 ppm (t, 3H, J=7.5 Hz).

By the same procedure, *N*-benzylidene-*n*-propylamine (50 g, 0.34 mol) gives dried, distilled *n*-propylamine-*Nd*$_2$; yield: 14.9 g (72%); b.p. 48–49 °C/750 torr.

I.R. (CCl_4): ν=2950; 2110; 1440; 1360; 1190; 990; 950 cm^{-1}.

^{1}H-N.M.R. (CCl_4): δ=2.60 (t, 2H, J=7.5 Hz); 1.45 (m, 2H); 0.85 ppm (t, 3H, J=7.5 Hz). Addition of H_2O to the ^{1}H-N.M.R. sample gives rise to a broad, 2H singlet at δ=1.72 ppm.

Lithium/Ethylamine Reduction; Typical Procedure:

Ethylamine (35 ml) is distilled from lithium (blue solution) into a dry, 100-ml three-neck, round-bottom flask cooled to −78 °C and provided with a magnetic stirring bar and rubber septum inlets. Lithium shot[9] (260 mg, 37 mmol), with freshly crushed surfaces, is added in one portion. After the mixture has been stirred for 30 min at −78 °C (blue color for at least 20 min), a solution of cholest-4-en-3-one (**1**; 530 mg, 1.38 mmol) and *t*-butanol (1.04 g, 14 mmol) in tetrahydrofuran (8 ml) is added dropwise by syringe. After stirring for an additional 30 min at −78 °C, water (5 ml) is added (disappearance of blue color), and the mixture is allowed to warm to room temperature. When most of the amine has evaporated, additional water is added *(cautiously, because some lithium particles may remain)*, and the mixture is extracted with ether to recover the product. Passage through EM Silica Gel 60 with ether/pentane removes a small amount of yellow, polar (probably dimeric) byproduct. Crystallization of the concentrated eluate from methanol/ether affords 5α-cholestan-3-one (**2**), homogeneous by T.L.C.; yield: 491 mg (92%); m.p. 130–131.5 °C (Lit.[10] m.p. 129–130 °C).

M.S. (30 eV): m/e (%)=385 (2.0); 386 (66.2, M$^+$); 387 (25.7); 388 (6.1).

Reductions of the other enones in the Table are conducted similarly, except that for the lower molecular weight enones the mol ratio of lithium:*t*-butanol:enone is decreased to ~10:5:1. Less ethylamine is also used in larger scale runs.

Reduction of **1** with lithium/ethylamine-*Nd*$_2$ and *t*-butanol-*Od* (Aldrich, 98+ atom %) affords, after refluxing the product with methanol/sodium methoxide (25:1) for 1 h, passage through EM

Silica Gel 60, and crystallization from methanol/ether, 5α-deuteriocholestan-3-one, homogeneous by T.L.C.; yield: 88%; m.p. 130.5–131 °C (Lit.[5] m.p. 129.5–130 °C).

M.S. (30 eV): *m/e* (%) = 386 (2.2); 387 (68.1, M^+); 388 (24.3); 389 (5.4).

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[7] 5α-Deuteriocholesta-1,3-diene, m.p. 60–61.5 °C, $\lambda_{max}^{hex} = 262$ nm ($\varepsilon = 3690$), derived from this enone by the method reported[6], shows $\Delta\varepsilon_{260}^{hex} = -1.85$, compared to $\Delta\varepsilon_{260}^{hex} = -2.10$ for a similarly prepared and purified sample of 5α-cholesta-1,3-diene, m.p. 60–60.5 °C, $\lambda_{max}^{hex} = 262$ nm ($\varepsilon = 3710$). Thus the $\Delta\varepsilon$ of the 5α-D diene is ~12% weaker than that of the 5α-H diene $[1 - (-1.85/-2.10) = 0.119]$.

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