Reduction of Cyclic Ureas with Lithium Aluminum Hydride

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A series of 1,3-dialkyl-2-imidazolidinones **1** and 1,3-dialkyltetrahydro-2(1*H*)-pyrimidinones **2** were reduced to the corresponding aminals **3** and **4**, respectively, when treated with excess lithium aluminum hydride in ether. The rate of reduction is affected dramatically by the alkyl substituents and slightly by ring size. Although lithium aluminum hydride reduces cyclic ureas under relatively mild conditions, reduction of ureas occurs less readily than reduction of other carbonyl compounds.

In connection with an ongoing investigation concerning the synthesis of biotin,[1] we required reliable information on the reactivity of certain cyclic ureas toward lithium aluminum hydride. Although isolated examples of the reduction of cyclic ureas by lithium aluminum hydride have been described, no systematic study of this reaction has been conducted. Accordingly the objective of the present investigation was to determine the facility with which cyclic ureas reduce and to define any substituent or steric effects.

Several 2-imidazolidinone and tetrahydro-2(1*H*)-pyrimidinone derivatives have previously been reduced with lithium aluminum hydride, generally in refluxing tetrahydrofuran or dioxane, but occasionally under milder conditions.[2-7] Reduction of cyclic ureas generally affords aminals, but reductive C–N bond cleavage has also been observed,[5,8,9] particularly with trisubstituted cyclic ureas.[4,10] Lithium aluminum hydride reduces the urea carbonyl of certain hydantoins (2,4-imidazolidinediones) and barbituric acids (tetrahydro-2,4,6-pyrimidinetriones).[11-15] Reduction of acylic di- and trisubstituted ureas has also been studied.[16-18]

Results and Discussion

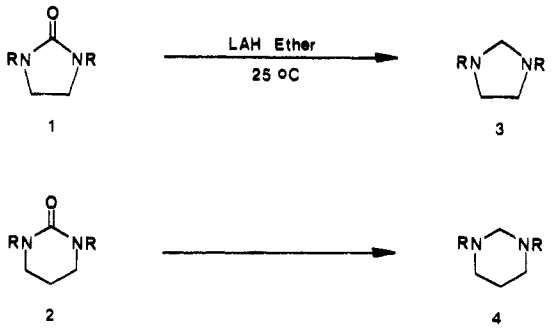
The 1,3-dialkyl-2-imidazolidinones **1b–d** and 1,3-dialkyltetrahydro-2(1*H*)-pyrimidinones **2b–d** required for this investigation were prepared by N-alkylation of 2-imidazolidinone (**1a**) and tetrahydro-2(1*H*)-pyrimidinone (**2a**), respectively. Sodium hydride was utilized as the base in DMF[19] or more conveniently in dioxane.[20] 1,3-Diphenyl-2-imidazolidinone (**1e**) was prepared from *N,N*-diphenyl-1,2-ethanediamine and chloral hydrate.[21]

Table I. Reduction of Cyclic Ureas with Lithium Aluminum Hydride[a]

urea	R	aminal	yield, %[b]	$t_{1/2}$, min	ref[c]
1b	Me	**3b**	58	10	26
1c	Et	**3c**	35[b]	60	27
1d	Bn	**3d**	89	5	28
1e	Ph	**3e**	71[d]	<2	29
2b	Me	**4b**	50	30	30
2c	Et	**4c**	12[b]	200	30
2d	Bn	**4d**	77	10	31

[a] Ureas were reduced with 500 mol % solid lithium aluminum hydride at 25 °C for 1 h in ethyl ether. [b] Isolated yields, except for reduction of **1c** and **2c** which was incomplete after 1 h. Partial loss of volatile products occurs during isolation. [c] Reference describes characterization of aminal. [d] Isolated after 8 min.

Excess lithium aluminum hydride in ether at 25 °C reduced cyclic ureas **1** and **2** to the corresponding cyclic aminals **3** and **4** (Table I). Reduction in refluxing tetrahydrofuran afforded the same products. The use of pure



lithium aluminum hydride is essential. Lithium aluminum hydride which had become slightly hydrolyzed by exposure to atmospheric moisture reduced the ureas much more slowly or not at all, even though it did reduce ketones and esters.

In order to define the stoichiometry, 1,3-dibenzyl-2-imidazolidone (**1d**) was reduced with a titrated solution of lithium aluminum hydride in ether. Complete reduction required 100 mol % lithium aluminum hydride (i.e., 4 hydride equiv). Two equivalents of hydride are consumed

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in the reduction, in accord with the reduction of tertiary amides.[22] The remaining 2 equiv of hydride do not reduce additional urea even after a protracted reaction period (50 h) but are released as hydrogen upon aqueous workup. When less lithium aluminum hydride was utilized, correspondingly less urea was reduced to aminal, and hydrogen was still evolved upon workup.

The rate of reduction of cyclic ureas **1** and **2** was affected by the alkyl substituents and by the ring size. By quenching the reductions before complete reduction we were able to estimate the reaction half-lives (Table I). The ease of reduction is phenyl > benzyl > methyl > ethyl. This order of reactivity, which is in accord with the reactivity of *N*-phenyl, *N*-benzyl, and *N*-alkyl amides,[23] may be attributed to the electron-withdrawing nature of the phenyl substituent which decreases amide resonance stabilization of the carbonyl group, thereby increasing its susceptibility toward nucleophilic attack. The ease with which *N,N*-dimethyl-2-imidazolidinone (**1b**) reduces must be a consequence its steric accessibility.

The 1,3-dialkyl-2-imidazolidinones **1** are reduced approximately twice as rapidly as the 1,3-dialkyltetrahydro-2(1*H*)-pyrimidinones **2**. Interestingly, the relative reactivity of cyclic ketones is opposite: Cyclohexanone is reduced 23 times faster than cyclopentanone.[24] Torsional strain, which is held responsible for the slower reduction of cyclopentanone than cyclohexanone,[24,25] is evidently less significant in cyclic ureas than in cyclic ketones. Five-membered urea **1d** presumably reacts more rapidly because change in hybridization from sp^2 toward sp^3 in the transition state releases more bond angle strain in five-membered rings than in six-membered rings.

Although cyclic ureas are reduced by lithium aluminum hydride under relatively mild conditions, they are reduced less readily than other carbonyl compounds. Thus lithium aluminum hydride completely reduces the lactam 1-methyl-2-piperidone with a half-life of less than 2 min, at least an order of magnitude faster than the corresponding urea **2b**. Even the most reactive urea studied, **1e**, was not reduced by ethanolic sodium borohydride[18] after 4 days at 25 °C or by diisobutylaluminum hydride in toluene and methylene chloride after 5 h at 25 °C.[1]

Experimental Section

General. Lithium aluminum hydride was purchased from Aldrich Chemical Co. and stored under anhydrous conditions. Ether was distilled from sodium and benzophenone. For stoichiometric experiments, an ether solution of lithium aluminum hydride was prepared and titrated by evolution of hydrogen upon treatment with water.

Tetrahydro-2(1*H*)-pyrimidinone (2a) was prepared from 1,3-propanediamine and urea.[32] The original condensate must be heated to its melting point to obtain the desired product, mp 258–263 °C (lit.[32] mp 258–262 °C). Less directly, **2a** was prepared by oxidation of tetrahydro-2(1*H*)-pyrimidinethione with hydrogen peroxide (618 mol %) and NaOH (300 mol %) at 0 °C and then at 70 °C for 30 min.[20] This compound is also commercially available.

General Procedure for Alkylation of Cyclic Ureas 1a and 2a.[20] A mixture of cyclic urea **1a** or **2a** (11 mmol), NaH (74 mmol) and dioxane (25 mL) was refluxed for 1.5 h. The suspension was cooled to 20 °C, and ethyl iodide (65 mmol) or benzyl bromide (23 mmol) was added. This mixture was refluxed for 3.5 h, cooled, and filtered. The solvent was evaporated from the filtrate, to afford the product which was purified by Kugelrohr distillation or recrystallization (71–83 % yield). Physical and spectral properties were in accord with the literature values.[19,20] 1,3-Dimethyl ureas **1b** and **2b** are commercially available.

1,3-Dibenzyltetrahydro-2(1*H*)-pyrimidinone (2d) was recrystallized from benzene (83 % yield): mp 82–85 °C; NMR ($CDCl_3$) δ 1.77 (2 H, p), 3.08 (4 H, t, NCH_2), 4.59 (4 H, s, NCH_2Ph), 7.2 (10 H, s, Ar); mass spectrum, *m/e* (relative intensity) 280 (M^+, 90), 189 (94), 91 (100); exact mass calcd for $C_{18}H_{20}N_2O$ 280.1577, found 280.1578.

1,3-Diphenyl-2-imidazolidinone (1e) was prepared as described,[21] except that chloral hydrate rather than chloral was utilized: mp 208–210 °C (lit.[21] mp 209–210 °C); NMR ($CDCl_3$) δ 3.95 (4 H, s), 7.0–7.7 (10 H, m).

General Procedure for Reduction of Cyclic Ureas 1 and 2. A mixture of pure lithium aluminum hydride (approximately 5 mmol) and cyclic urea **1** or **2** (1 mmol) in anhydrous ether (6 mL) was stirred for 1 h at 25 °C. The reaction was quenched with water (0.19 mL), 15% aqueous NaOH (0.19 mL), and water (0.57 mL). The precipitate was removed by filtration and washed with ether. Evaporation of the ether afforded aminals **3** or **4**, respectively, which were purified by Kugelrohr distillation. Physical and spectral properties were in accord with the literature values (Table I). To determine reaction rates, reductions were quenched after shorter reaction times, typically 8 min. Ratios of starting material to product, determined by NMR, were utilized to calculate the half-lives.

1,3-Dibenzylhexahydropyrimidine (4d): Kugelrohr distillation, bp 140–150 °C (0.4 torr) [lit.[31] bp 110–120 °C (0.03 torr)]; NMR ($CDCl_3$) δ 1.52 (2 H, p), 2.50 (4 H, t, NCH_2), 3.18 (2 H, s, NCH_2N), 3.54 (4 H, s, NCH_2Ph), 7.1 (10 H, s, Ar).

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