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THE REACTION OF SUBSTITUTED UREAS WITH SODIUM BOROHYDRIDE IN PYRIDINE

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We have been investigating new types of reactions with sodium borohydride,[1] the reagent, a combination of sodium borohydride and pyridine, showed a very interesting reaction. The reduction of amides with this reagent was reported[1a)1g)] to give the corresponding amines and nitriles by two of the present authors (S.Y. and Y.K.). In this communication, we wish to report the reduction of ureas, which gives different results as compared with those of carboxylic acid amides, utilizing the sodium borohydride and pyridine combination.

We examined the reduction of 1,3-disubstituted, 1,1,3-trisubstituted and 1,1,3,3-tetrasubstituted ureas using the reagent mentioned above, and different kinds of reductions were found to be carried out depending on the number of substituents.

A) The Reduction of 1,3-Disubstituted ureas with Sodium borohydride

Treatment of 1,3-disubstituted ureas I with ca. 1.2 molar equivalents of sodium borohydride in refluxing pyridine gives the corresponding amidine II in moderate yields, as shown in the Table I. When the substituents are aliphatic groups, the yields of amidine are generally better than those of the aromatic group. In the case of 1,3-diphenylurea, yields were not improved in spite of

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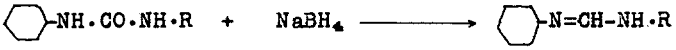
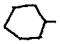
the investigations carried out under various conditions.



I II

Table I

R	Urea I (mmoles)	$NaBH_4$ (mmoles)	Product Amidines II[a)] b.p.(m.p.)°C	Yield(%)	Picrate m.p.
	50	60	(100-102)	66.8	220
CH_3 / C_2H_5 > CH-	30	36	(70)	56.3	168
$(CH_3)_3C$-	30	36	15mmHg,112-115	45.3	196
CH_3 / CH_3 > CH-	30	36	4mmHg,90-95(70)	64.8	173
C_6H_5	20	30	(116)	17.5	206-207

a) Satisfactory analytical data have been obtained for all the amidines.

Typical Procedure —— A solution of 1,3-dicyclohexylurea (11.22g., 50 mmoles) and sodium borohydride (2.27g., 60 mmoles) in dry pyridine (125 ml.) was refluxed for 25 hr. After the reaction was complete, pyridine was removed under reduced pressure. The residue was dissolved in water (50 ml.) and the aqueous solution was extracted with benzene. After drying over anhyd. Na_2SO_4, benzene was removed leaving a residue which was recrystallized from cyclohexane. N,N'-Dicyclohexylformamidine (m.p. 100-102°C, yield 6.95g., 66.8%) was obtained. This compound was identified with the authentic sample by its mixed melting point.[8d)]

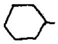
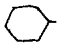
Several methods for the preparation of N,N'-dicyclohexylformamidine have been reported[8)], however, the method starting from 1,3-dicyclohexylurea and sodium borohydride seems to be the simplest, as compared with other methods, and should be one of considerable synthetic utility.

B) The Reaction of 1,1,3-Trisubstituted Ureas with Sodium borohydride

The attempted reaction of 1,1,3-trisubstituted ureas with sodium borohydride under the same procedure as above has led to quite different results from those of 1,3-disubstituted urea. In this case, the precipitated adduct was first formed in the reaction course. Decomposition of the adduct with water gave two products, a neutral compound, formamide IV in 40-80% yield and a basic compound, secondary amine, though the structure of the adduct is not yet clear. N,N,N'-Trisubstituted formamides were not obtained in every case. Therefore, fission of the C-N bond of ureas generally takes place at the bond between the disubstituted nitrogen atom and the carbonyl carbon atom.

$$\underset{\text{III}}{RNH{\cdot}CON{<}^{R'}_{R'}} + NaBH_4 \xrightarrow{\text{pyridine}} \text{Adduct} \xrightarrow{H_2O} \underset{\text{IV}}{RNH{\cdot}CHO} + \underset{\text{V}}{NH{<}^{R'}_{R'}}$$

Table 2

R	R'	Product[a)] Formamide Yield(%)	Formamide b.p.°C	Secondary Amine Yield(%)	Secondary Amine b.p.°C
		64	3mm.Hg. 117	70	40mm.Hg. 145
"	C_2H_5-	79	3mm.Hg. 114-116	c)	
C_6H_5-	"	42	3mm.Hg. 110	c)	
n-C_4H_9-	"b)	66	8mm.Hg. 110-111	c)	
"	n-C_4H_9-b)	49	17mm.Hg. 120-125°	c)	

a) Products were identified by their similarity in IR spectra with authentic samples.

b) Precipitated adducts were not obtained, therefore, after evaporation of pyridine the residue was treated with water.

c) The expected diethyl- and dibutyl- amines could not be isolated probably due to their low boiling points.

Typical Procedure ——— A solution of 1,1,3-tricyclohexylurea (9.20g., 30 mmoles) and sodium borohydride (1.36g., 36 mmoles) in dry pyridine (75 ml.)

was refluxed for 20 hr. Its precipitated adduct, which was decomposed with water (100 ml.), was filtered and the aqueous solution was acidified with concentrated hydrochloric acid at pH 4.0. Insoluble dicyclohexylamine hydrochloride was filtered and from this free dicyclohexylamine (3.81g, 70%) was obtained by the usual method. The filtrate was extracted several times with benzene. Benzene was removed and the residual oil was distilled to give N-cyclohexylformamide (2.31g, 64%).

Reactions of 1,1,3,3-tetrasubstituted ureas, such as 1,1,3,3-tetracyclohexylurea and 1,1,3,3-tetra-n-butylurea, with sodium borohydrid under the same procedure were unsuccessful even after long refluxes, more than 90% of the starting material was recovered.

Studies of the scope and limitation of this reaction on open chain and cyclic urea derivatives are in progress.

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