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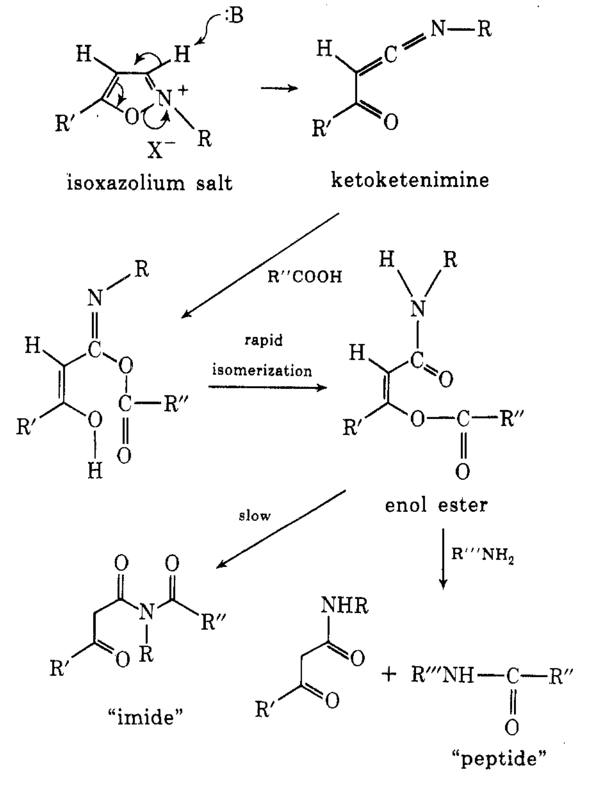
Communications

A Facile Conversion of Carboxylic Acids to Carbinols under Mild Conditions[1]

Summary: Enol ester derivatives, produced upon treatment of carboxylic acids with *N*-ethyl-5-phenylisoxazolium 3′-sulfonate, afford carbinols upon reduction with sodium borohydride in aqueous solution.

Sir: In a reinvestigation of isoxazolium salts, originally reported by Otto Mumm,[2] Woodward and coworkers[3-5] showed that a number of 3-substituted isoxazolium salts react with carboxylic acids in the presence of a base to yield enol ester derivatives which are useful acylating agents, especially in peptide synthesis. The principal features of this chemistry are indicated in Scheme I.

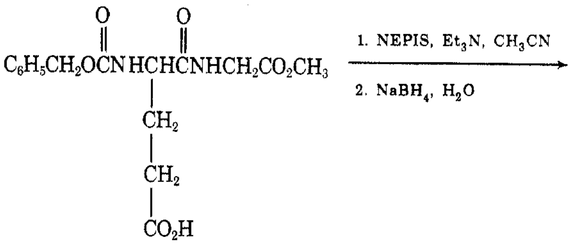
Scheme I



In conjunction with our studies on the catalytic roles of carboxyl groups in the active sites of enzymes, we required a means by which such carboxyl groups could be reduced to carbinol groups. Clearly, the conventional methods employing lithium aluminum hydride or sodium borohydride–aluminum chloride could not be employed for protein modification in aqueous solution. However, recent reports on the use of Woodward's isoxazolium salts in aqueous solution to activate carboxyl groups in enzymes toward attack by various nucleophilic reagents[6-8] suggested that perhaps activation of such carboxyl groups toward reduction by aqueous sodium borohydride might be similarly achieved. The preliminary investigations reported here show that such is indeed the case.

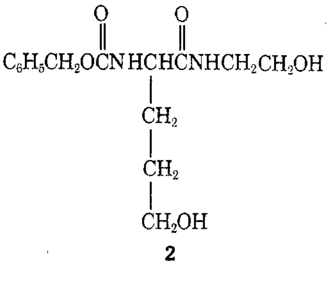
Enol ester derivatives of the acids in Table I were prepared essentially as described by Woodward, *et al.*,[5] using *N*-ethyl-5-phenylisoxazolium 3′-sulfonate[9] (NEPIS) with triethylamine as the derivatizing agent in acetonitrile solution at room temperature. The crude enol esters were then freed of solvent *in vacuo*, dissolved in water, and treated with a 10-fold molar excess of sodium borohydride.[10] Carbinol yields (Table I) varied from 40 to 100%.

The peptide derivative 1 (*O*-methyl *N*-benzyloxycarbonyl-α-L-glutamylglycinate) was prepared as a model substrate to test the applicability of our reduction proce-



$$C_6H_5CH_2O\overset{O}{\overset{\|}{C}}NH\underset{\underset{\underset{\underset{\underset{\underset{CO_2H}{|}}{CH_2}}{|}}{CH_2}}{|}}{C}H\overset{O}{\overset{\|}{C}}NHCH_2CO_2CH_3 \xrightarrow[2.\ NaBH_4,\ H_2O]{1.\ NEPIS,\ Et_3N,\ CH_3CN}$$

1



$$C_6H_5CH_2O\overset{O}{\overset{\|}{C}}NH\underset{\underset{\underset{\underset{\underset{\underset{CH_2OH}{|}}{CH_2}}{|}}{CH_2}}{|}}{C}H\overset{O}{\overset{\|}{C}}NHCH_2CH_2OH$$

2

Table I
Conversion of Carboxylic Acids to Carbinols by NEPIS Activation in Acetonitrile Followed by Sodium Borohydride Reduction in Water

Acid	Carbinol	Method[a]	Yield, %
CH_3COOH	CH_3CH_2OH	A	90[b]
C_6H_5COOH	$C_6H_5CH_2OH$	A	94[b]
$CH_3CH_2CH_2COOH$	$CH_3(CH_2)_3OH$	A	100[b]
$CH_3(CH_2)_{15}COOH$	$CH_3(CH_2)_{16}OH$	B	50[c]
$CH_2{=}CHCOOH$	$CH_3CH_2CH_2OH$	A	100[b]
$HSCH_2COOH$	$HSCH_2CH_2OH$	A	80[b]
$C_2H_5O_2C(CH_2)_4COOH$	$C_2H_5O_2C(CH_2)_5OH$	B	71[d]
$(C_6H_5)_2CHCOOH$	$(C_6H_5)_2CHCH_2OH$[e]	B	40[f]

[a] See Experimental Section for detailed description of the methods employed.[12] [b] Identification and quantitation by comparison of glpc chromatograms of product mixtures with those of standard solutions of authentic carbinols. [c] Isolated yield, mp 48–49° [mp 49°: S. G. Ford and C. S. Marvel, *Org. Syn.*, **10**, 62 (1930)]. Micelle formation made extraction of this carbinol from the aqueous product mixture extremely inefficient and may account in part for the low isolated yield. [d] Isolated yield, $n^{24}\text{D}$ 1.4276 [$n^{24}\text{D}$ 1.4275: R. Huisgen and J. Reinertshober, *Justus Liebigs Ann. Chem.*, **575**, 174 (1952)]. [e] Accompanied by *N*-ethyl-α,α-diphenylacetamide (35% yield) identified by ir, nmr, and mass spectrum (*m/e* 237) and mp 134–135° [mp 134.5–135.5°: D. B. Limaye and T. B. Pause, *Rasayanam*, **2**, 32 (1950)]. [f] Isolated oil had identical glpc retention time and tlc R_F value as authentic 2,2-diphenylethanol, mp 58–59° [mp 59°: P. S. Hammick, Jr., and C. R. Hawser, *J. Org. Chem.*, **26**, 4199 (1961)], prepared from diphenylacetic acid by the method of N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).

dure to free carboxyl groups in peptides or proteins. Compound 1 was synthesized according to a published procedure for the corresponding ethyl ester.[11] The two-step reduction procedure (method A; see Experimental Section)[12] gave the diol derivative 2[13] in 50% yield. The free γ-carboxyl function of the glutamyl residue was reduced as expected. The concomitant reduction of the carboxyl-terminal methyl ester linkage of 1 finds ample precedent in the work of Yonemitzu, *et al.*,[14,15] in which it was determined that carboxylic esters having an α-amino function are subject to reduction by sodium borohydride. We in fact confirmed this with our finding that a direct reduction of 1 using aqueous sodium borohydride under the conditions employed to effect the second step in the production of 2 afforded a clean selective reduction of the terminal methyl ester group and was without effect upon the free carboxyl group, the peptide linkage, or the benzyloxycarbonyl moiety of 1. It should be noted, however, that simple esters which are not activated by the presence of an electron-withdrawing substituent in the α position are not subject to reduction by aqueous sodium borohydride. Thus, treatment of ethyl heptanoate with $NaBH_4$ under the conditions employed in this investigation for the reduction of enol ester derivatives resulted in 96% recovery of the original ester. Also, in the reduction of monoethyl adipate (Table I) the ethyl ester function was not reduced during conversion of the free carboxyl group to the carbinol.

Finally, the low yield of carbinol realized in the reduction of diphenylacetic acid (Table I) and the finding that the 2,2-diphenylethanol produced in this reduction was accompanied by a roughly equivalent yield of *N*-ethyl-α,α-diphenylacetamide suggest that the reduction of NEPIS enol esters may not always be so straightforward as originally envisaged. As shown in Scheme I, the enol esters derived from carboxylic acids by treatment with isoxazolium salts are subject to isomerization *via* an O- to N-acyl shift to give the imide. This isomerization is accelerated by bases[3] and, under the alkaline conditions which accompany aqueous $NaBH_4$, imide formation might be quite rapid. Thus isomerization would be expected to compete to some extent with direct reduction of the enol ester by $NaBH_4$, especially when borohydride attack is sterically hindered as would be the case for the NEPIS enol ester of diphenylacetic acid. The imide products of base-catalyzed isomerization may themselves be subject to reduction by $NaBH_4$. Borohydride reductions of cyclic imides are known,[16-19] with borohydride attack directed preferentially to the less hindered carbonyl group, giving rise to an amide and a carbinol. This would account for the observed amide production which was found to accompany 2,2-diphenylethanol formation in our attempted reduction of diphenylacetic acid.

Experiments directed toward a more definitive elucidation of the chemistry presented in this communication and toward its application in the reduction of carboxyl groups in proteins and carbohydrates are currently in progress. The procedures described here may also find application in general organic synthesis involving the reduction of carboxyl groups in multifunctional compounds which will not tolerate the reagents and conditions conventionally employed in carboxyl group reductions.

Supplementary Material Available. The experimental procedures used in this investigation will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-111.

References and Notes

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