

Table I. Overall Barrier Height (ΔE) for the $C_2H_4 + BH_3$ Reaction

method ^a	ΔE , kcal/mol	method ^a	ΔE , kcal/mol
4-31G	11.7	4-31G + CI (S + D + Q)	5.6
4-31G + CI (S + D)	9.7	exp ^b	2 ± 3
6-31G**	6.7		

^a S = single excitation, D = double excitation, and Q = quadruple excitation. ^b Reference 15.

plex has to pass over a substantial energy barrier to complete the reaction, and this should be the rate-determining step for the overall reaction. The calculated SCF overall barriers of 11.7 (4-31G) and 6.7 (6-31G**) kcal/mol are, as expected, too large, compared with a gas-phase experimental estimate (2 ± 3 kcal/mol)¹⁵ determined indirectly from an Arrhenius plot of the relative peak areas of mass spectra. We have carried out CI calculations including all the single and double excitations relative to the SCF reference configuration, except that the core orbitals are frozen. The unlinked quadruple-excitation contribution to the correlation energy was estimated further with the Davidson method.¹⁶ The results are summarized in Table I. Though not actually carried out, the best calculation, an S + D + Q CI with the 6-31G** basis set, is expected to give a barrier of ~ 4 kcal/mol which is in reasonable agreement with the experimental estimate.

In conclusion, the hydroboration reaction proceeds through a two-step process. First, a loose three-center π complex is formed in the early stage without an energy barrier, and then it is transformed to the product via a four-center transition state, this process being the rate-determining step. The overall mechanism proposed is significantly different from any previous study, though it in part supports some of previous findings. Details of the study will be published elsewhere.

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Shigeru Nagase, N. K. Ray, Keiji Morokuma*

*Institute for Molecular Science
Myodaiji, Okazaki 444, Japan*

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Peptide Synthesis Using Unprotected Amino Acids and Novel Imidoyl Halide Reagents

Sir:

We report herein the synthesis and use of new imidoyl halide reagents for condensation reactions (including peptide synthesis). The reagents have the important advantage that (a) it is not necessary to protect amino acids using blocking agents, (b) racemization is minimal, (c) reaction conditions are particularly mild, and (d) competing reactions (such as intramolecular O \rightarrow N acyl group migration) are suppressed.

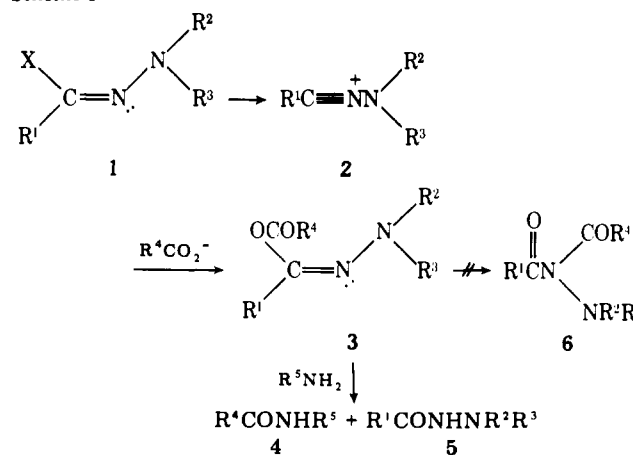
Imidoyl halides **1** on dissolution in polar solvents undergo rapid unimolecular ionization to give the nitrilium ions **2** (Scheme I). These ions are highly selective (as shown by large common ion effects) and undergo stereospecific reaction at carbon with nucleophiles.^{1,2} Thus only the isomer (e.g., **3**) in which the incoming nucleophile and forming lone pair on nitrogen are trans is formed.

We have now found that nitrilium ions are unusual in that they react more rapidly with carboxylate ions than with simple amines.³ Scheme II summarizes some typical rate data for imidoyl halide **1a**. It is clear that, when acetate and the amine (morpholine) are present in equal concentrations, the major product formed is still the *O*-acylisoamide **8** rather than the amidine **9**. This competition can be further altered in favor of the isoamide **8** by pH control. For example, when trapping of the nitrilium ion is carried out at pH 6 (>2 pH units below the pK_a of the amine), >99% of the trapped product formed is the isoamide **8** (in the presence of equal concentrations of acetate and morpholine). However the nitrilium ion discriminates between H_2O and AcO^- (see Scheme II); thus the trapping reactions can be carried out in aqueous solution.⁴

The *O*-acylisoamide **3**, once formed by selective trapping, shows the normal reactivity expected from an activated ester. Thus the rate of reaction of **3** with carboxylate ion is negligible in basic solution when compared with its reactivity toward amines (yielding the amide **4**). The formation of the amides (or peptides) **4** can therefore be carried out by adding the halide **1** to a solution containing both amine (R^5NH_2) and carboxylate ($R^4CO_2^-$). The initial reaction (formation of the adduct **3**) is best carried out at pH ~ 6 ; when the pH is adjusted to ~ 8 , formation of the amide **4** is rapid and complete.

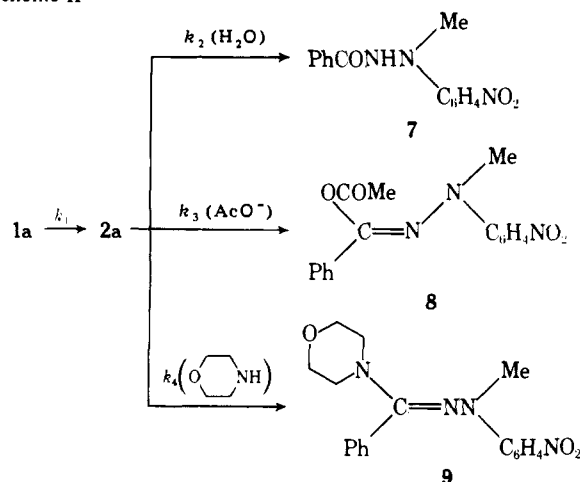
A vital feature of the reagent **1** is that the intermediates **3** are stable toward O \rightarrow N acyl group rearrangement (to give

Scheme I



	R ¹	R ²	R ³	X
a	Ph	Me	<i>p</i> -NO ₂ C ₆ H ₄	Cl
b	Ph	Me	Ph	Br
c	CMe ₃	Me	Ph	Cl

Scheme II



rate constants (measured in 4:1 dioxane-water at 25 °C):
 $k_1 = 8.6 \times 10^{-2}/s^{-1}$; $k_3/k_2 = 1100$; $k_3/k_4 = 6$; $k_4/k_2 = 160$

the unreactive *N*-acyl amide **6**). This is ensured by (a) the stereospecific formation of **3** and (b) by the presence of a group (NR^2R^3) attached to the imino nitrogen which slows the rate of inversion of this nitrogen.⁵ Consequently, the acyl group and the lone pair on the adjacent nitrogen are mutually trans which inhibits intramolecular rearrangement and stabilizes intermediate **3**. Because of the relative stability of **3** it is possible to complete its formation with one carboxylic acid (or amino acid) before the amine (or a second amino acid) is added.

Since the intermediate **3** is an activated ester, the possibility of racemization α to the carboxylate function of an amino acid during peptide synthesis arises. This was tested using the Anderson method.⁶ With reagent **1b** some racemization did occur, but this was pH dependent (21% racemate at pH 9.3, 2.5% at pH 7.8, and 1.0% at pH 7.2) consistent with racemization occurring via base-catalyzed isoxazoline formation.⁷ It is thus an obvious advantage when chiral reagents are used to maintain the pH of the coupling medium ≤ 7 . We have also found that racemization can be suppressed by varying the substituent (R^1) attached to carbon in the halide **1**. The most successful modification is the incorporation of a *t*-Bu group at this position. Using reagent **1c** we were unable to detect any racemization even at pH 9.5 (using the Anderson test).⁸

Although the highly selective nature of the reaction means that unprotected amino acids can be used, it is advisable to protect the nitrogen of the *first* amino acid (by, for example, a carbobenzyloxy group). This has two advantages: (a) separation of the carbobenzyloxylated peptide is facilitated; (b) intramolecular reaction of the growing peptide chain (which can be expected on going from two to three amino acid units) is suppressed.

Besides the advantages listed above, the imidoyl halide reagents **1**, unlike the related carbodiimides,^{7b} make the nitrilium ion **2** available at all pH's without the necessity of acid or base catalysis. Moreover the hydrazide **5** formed during reaction can be recovered and reconverted to the active imidoyl halide reagents **1** and thus recycled.

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preliminary data which indicates that the reactions of both species with the nitrilium ion may be diffusion controlled.

- (4) We have typically used solvents in the range of 1:1 to 9:1 dioxane-water or acetone-water, the lower aqueous contents being used with the more reactive halides **1**.
- (5) The rate of isomerization of *O*-acylsolmides of type **3** to **6** has been shown to be limited by the rate of *Z* to *E* isomerization about the C=N bond; see ref. 1 and D. G. McCarthy and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1080 (1977).
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- (10) Address correspondence to the Chemistry Department, University College, Belfield, Dublin 4, Ireland.

A. F. Hegarty,*¹⁰ D. G. McCarthy

Chemistry Department, University College, Cork, Ireland

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Monomeric Molybdenum Oxo Complexes with Tetradentate Aromatic Aminothiols. Model Redox Systems for Molybdenum Enzymes

Sir:

Molybdenum enzymes catalyze the transfer of electrons between a donor or acceptor and substrate. For oxidases and dehydrogenases, the evidence indicates substrate is oxidized in an irreversible two-electron step, with the molybdenum center undergoing initial reduction from the VI to the IV state.¹⁻³ Reoxidation by other cofactors (FAD, Fe_2S_2) occurs in two one-electron steps via an EPR active Mo(V) state with xanthine oxidase.⁴ Electron transfer between the reduced Mo(IV) center and the Fe_2S_2 and FAD centers of this enzyme is rapid, with the distribution of electrons between the various oxidation states of each cofactor at a given level of enzyme reduction governed by their reduction potentials.^{1,4,5}

The electrochemistry of a number of molybdenum(VI) dioxo and monomeric molybdenum(V) oxo complexes has been investigated.^{6,7} The Mo(VI) complexes appear to be electrochemically reducible (usually irreversibly) to the IV state⁶ but not, in general, to the V state.^{7,8} Furthermore, monomeric molybdenum(V) oxo complexes that have been studied are not electrochemically oxidizable to the VI state.⁷

In the course of a study of monomeric molybdenum(V) oxo systems as enzymatic models, we have prepared two new complexes ($MoOL^-$) with tetradentate aromatic aminothiols

