dition, on a preparative scale a variety of heterocyclic condensed dihydroquinolone systems have now become accessible; for example, **7** (mp 197–199.5°) was obtained by the nonoxidative photocyclization of thiophen-2-carboxanilide in 56% yield. Synthetic applications of the method to other heterocyclic systems including furan, pyrrole, and their benzo derivatives are in progress.

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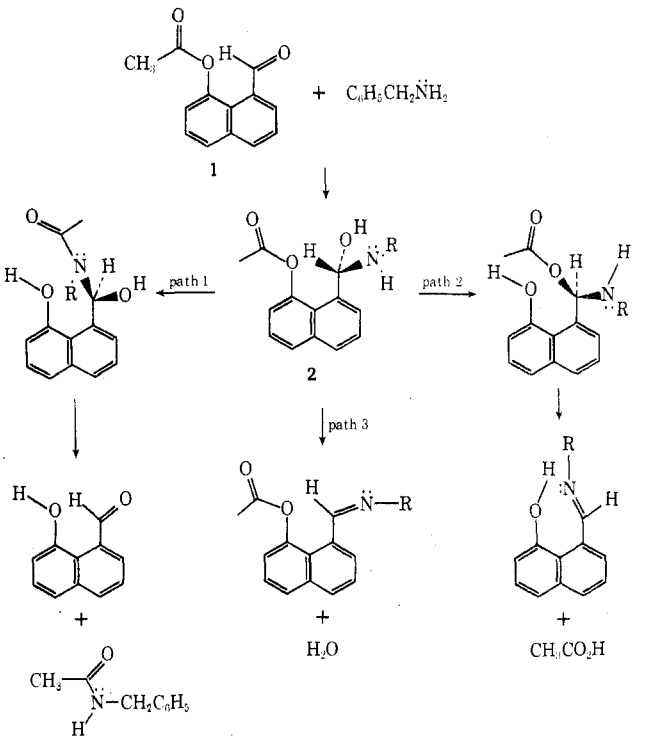
Rapid Intramolecular Acyl Transfer from Phenol to Carbinolamine—Progress toward a New Class of Peptide Coupling Reagent

Summary: Benzylamine and amino acid esters react with 8-acetoxy-1-naphthaldehyde, 2-acetoxybenzaldehyde, and 2-acetoxytrifluoroacetophenone with formation of carbinolamines, followed rapidly by solvent dependent *O*- or *N*-acyl transfer or dehydration.

Sir: We wish to report unusual, rapid intramolecular acyl transfer reactions via seven-ring intermediates, which represent the first step toward the development of a new class of peptide coupling reagent, as well as progress toward mimicking biochemical acyl transfer processes.

When 8-acetoxy-1-naphthaldehyde[1] (**1**) is treated with benzylamine (3 equiv, 1.2 *M*) in DMSO[2] a 70% yield of *N*-benzylacetamide is formed, together with 30% acetate ion; at 25° the half time is <1 min. We interpret this reaction as occurring via rapid formation of a carbinolamine, **2**,[3] followed by seven-ring intramolecular *N*- (path 1, amide formation) or *O*- (path 2, acetate ion formation) acyl transfer.



The product composition is strikingly solvent dependent, although in no instance could a single product be obtained. DMSO or DMF give 60–70% amide (path 1) and ~30% acetate (path 2); in 1:1 DMSO–water the ratio is 3:7, while in 1:4 acetonitrile–water, the ratio is 1:9. In other solvents dehydration of **2** to an acetoxy Schiff base (path 3) was observed. Thus in acetonitrile the ratio of products from paths 1 and 3 is 1:1; in benzene, carbon tetrachloride, or chloroform no amide is formed, and paths 2 and 3 contribute in respective ratios of 7:3, 7:3, and 1:4. Variation of the equilibrium between **2** and its zwitterion and chloroform catalysis of dehydration of **2** are presumably responsible for these results. Rate constants for the combined acyl transfer processes in acetonitrile, DMF, and 1:4 acetonitrile–water at 30° are 0.1, 0.2, and 15 M^{-1} sec^{-1}, respectively. The latter is one of the faster intramolecular acyl transfers reported for a model system.[4]

Though exact models are problematic, an estimate of the rate of intermolecular attack of amine on the acyl site of **1** is 1×10^{-3} M^{-1} sec^{-1}, observed for reaction of benzylamine and 8-acetoxy-1-nitronaphthalene[5] in acetonitrile at 30°. We note that the rapid formation of acetic acid and the Schiff base of 8-hydroxy-1-naphthaldehyde in anhydrous solvents is only consistent with intermediacy of **2** and its decomposition by path 2.

Marked changes in product composition also result with change of amine. Reaction of **1** with methyl alaninate or other substituted peptide amines yields only the product of path 3. This result excludes exploitation of derivatives of **1** in peptide synthesis.

It was hoped that the formyl group of an 8-acyloxy-1-naphthaldehyde could be protected as an acetal, and the resulting functionality employed in peptide synthesis as a C-terminal protective group[6] capable of activation under midly acidic conditions. Along with the virtues of latent activation, amide formation by amine capture and intramolecular acylation offers several intrinsic advantages over intermolecular acylation. (1) The ester function can hopefully be of a low degree of activation, minimizing side reactions.[7] (2) The amide forming step must follow first- rather than second-order kinetics. (3) Provided that the amine capture step is rate determining, the rate of amide forma-

tion should not be reduced by steric bulk at the acyl site.[8] (4) Intermediates such as oxazolones which are formed by fragmentation at the acyl site should compete ineffectively with intramolecular acylation.

Two other attempts to exploit carbinolamine intermediates further defined the scope of this principle.[9] Aminolysis of 2-acetoxybenzaldehyde (**3**)[10] with benzylamine in any of the above solvents gives benzylacetamide in quantitative yield. Most strikingly, rate constants nearly identical with those of **1** were observed in DMF, acetonitrile, and acetonitrile–water. Since the ester functions of **1** and **3** must differ in intrinsic activation[11] as aldehydes, but not when converted to carbinolamines, we argue from this result that **3** also must react with benzylamine via a carbinolamine intermediate. In acetonitrile, benzylamine reacts 150 times as rapidly with **3** as with 4-acetoxybenzaldehyde.[12]

Although a 90% conversion of ethyl glycinate to amide results from reaction with 1 equiv of **3** in benzene (75% in acetonitrile), with the more hindered methyl esters of alanine, phenylalanine, and valine, the sole products detected are the Schiff bases of **3**.

A third carbonyl derivative, 2-acetoxytrifluoroacetophenone (**4**),[13] was investigated in the hope that this species would form a less dehydration-prone carbinolamine. In fact, **4** reacts in benzene with any of the above amines with exclusive *O*-acyl migration, leading to quantitative formation of acetic acid. Half times were <1 min.

A noncovalent binding of an amine which maintains it in reactive proximity to a relatively unactivated aliphatic ester is the characteristic feature of biochemical peptide coupling.[14] The systems we have described can be regarded as models for this process in which noncovalent affinity is replaced by a covalent bond of the carbinolamine function.

The results achieved thus far for these systems are (1) a demonstration of at least a hundredfold catalysis over direct aminolysis, (2) a demonstration that with favorable geometry a seven-ring intermediate can achieve the catalytic advantage for acyl transfer of the more familiar six-ring cases, and (3) a demonstration that very great sensitivity of product ratio to amine bulk and solvent attends these reactions. This latter point has led us to seek systems which can trap amines at electrophilic sites to yield intermediates with less versatility than carbinolamines, and results of these studies will be reported subsequently.

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