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3,5-DIAMINO-6-CHLOROPYRAZINECARBOXYLIC ACID "ACTIVE ESTERS" AND THEIR REACTIONS (1)

Kenneth L. Shepard, Wasyl Halczenko, and Edward J. Cragoe, Jr.
Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
West Point, Pennsylvania

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Stable, yet highly reactive, acylating agents have broad application in a variety of areas in synthetic organic chemistry. Recent studies in our laboratories have shown N-t-butyl-3-(3,5-diamino-6-chloropyrazinecarbonyloxy)crotonamide (III) (2) and 3,5-diamino-6-chloropyrazinecarboxylic N,N-diphenylcarbamic anhydride (IX) to be stable crystalline species, yet these "active esters" acylate a wide variety of nucleophilic substances under relatively mild conditions.

The application to peptide synthesis of the activated esters formed from carboxylate anions and certain isoxazolium salts has been well documented (3,4,5). Although isolation and purification of the intermediate enol esters has been reported, these derivatives are somewhat unstable and are susceptible to an undesirable rearrangement. Recently, however, Woodward and Woodman reported the isolation of two stable crystalline esters from N-t-butyl-5-methylisoxazolium perchlorate (II) (6). It has now been discovered that similar derivatives, using pyrazinecarboxylic acids of interest to us, can be generated, isolated, and purified, permitting investigation of the general synthetic application of such esters.

The ester (III) generated *in situ* in DMF reacts with a variety of substituted hydrazines to give the corresponding hydrazides (VIa,b,c). Similarly, reaction occurred with aliphatic amines to give the corresponding amides, e.g., VId. When guanidine or aminoguanidine was used, the desired products (VIg,h) were obtained, however, the yields were

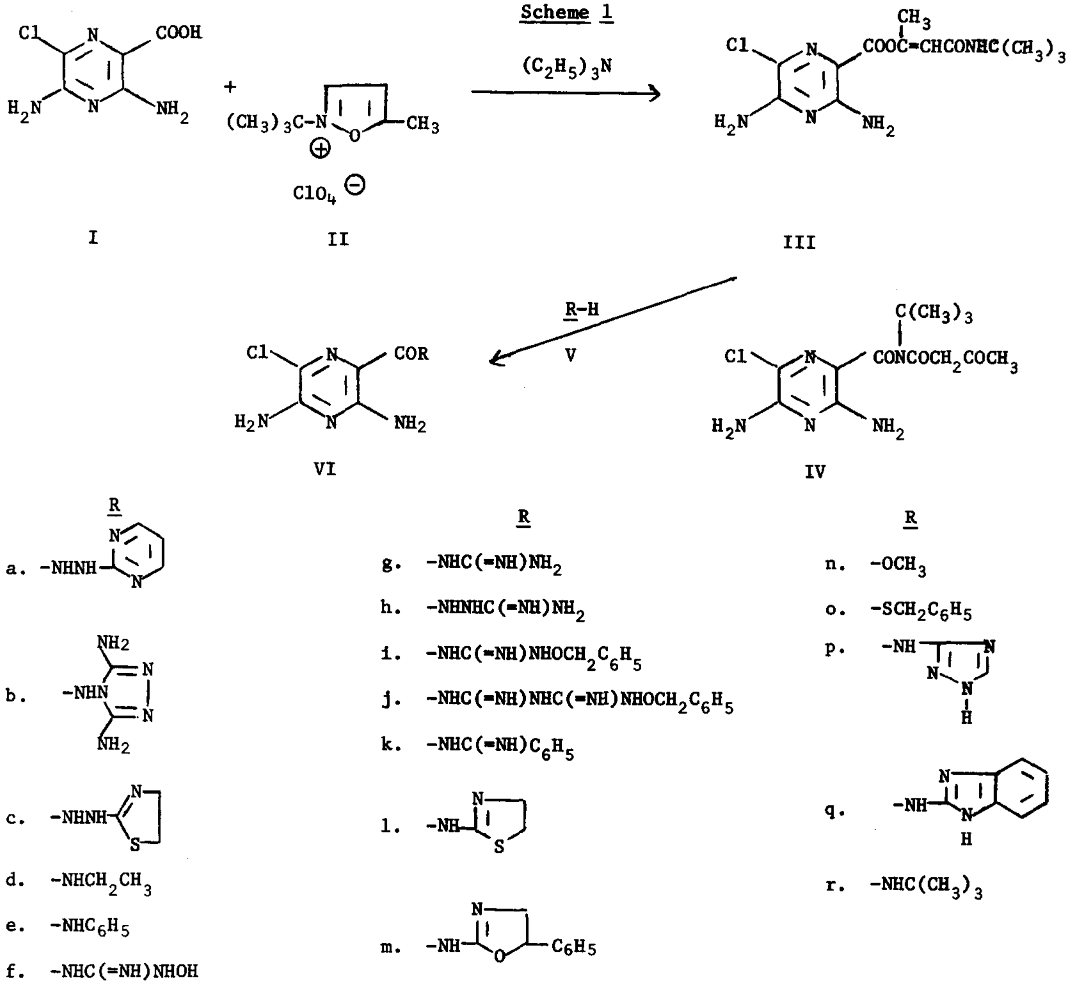
originally below 40%. Subsequent experiments with other strong bases, i.e. sodium alkoxides or sodium urea, in DMF or DMSO indicated that these conditions favored rearrangement of III to IV rather than the desired acylation (Woodward, et.al., describe an analogous rearrangement, 5). For example, treatment of III with sodium methoxide in DMF (or DMSO) for one-half hour produced IV; Anal. Calcd. for $C_{13}H_{18}ClN_5O_3$: C,47.63; H,5.53; N,21.37. Found: C,47.73, H,5.37; N,21.55. IR (KBr): 3490cm^{-1} ($-NH_2$), 3430cm^{-1} (broad, strongly bonded $-NH_2$), 1710 and 1685cm^{-1} (-CONCO-). NMR (CF_3COOH): τ8.25, singlet, $-C(CH_3)_3$; τ7.45, singlet, $-COCH_3$. When III was heated in DMF in the presence of triethylamine (24 hrs., 90°), a 40% yield of the t-butyl amide (VIr) was isolated; Anal. Calcd. for $C_9H_{14}ClN_5O$: C,44.35; H,5.79; N,28.74. Found: C,44.53; H,5.63; N,28.47. This product, most likely, arose through rearrangement of III to IV followed by subsequent cleavage to VIr. Thus, the decreased tendency towards rearrangement of enol esters derived from II is more likely a result of a large kinetic barrier, rather than a result of being the thermodynamically favored isomer (6).

When III was isolated and subsequently treated with sodium methoxide in methanol, the methyl ester (VIn) was produced in good yield. This indicated that the competing rearrangement of III to IV, observed under strongly basic conditions in DMF or DMSO, apparently was a result of the high polarity of the solvent.

As anticipated, the yields of products (VIf,g,h,i,j) from III and strong nitrogen bases were better (60-90%) when the ester was isolated and the reaction conducted in 2-propanol, tetrahydrofuran, or acetonitrile (7). In most cases, the conditions for preparation of the products listed in Scheme 1 involved refluxing III and V in one of these solvents for several hours, although formation of VIe required refluxing in n-amyl alcohol for twenty-four hours. The acylation of benzyl mercaptan and benzamidine (Vo,k) was accomplished in aqueous sodium hydroxide solution. The products listed in Scheme 1 give some measure as to the variety of nucleophiles which condensed with III (exceptions Vp,q).

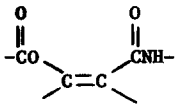
The failure of III to acylate very weak nucleophiles such as 3-amino-1,2,4-triazole or 2-aminobenzimidazole under any conditions employed initiated a search for an even more reactive acylating derivative of I. Since acyloxyacrylamides, VII, are "vinylogs" of carboxylic-carbamic mixed anhydrides, VIII, it seemed worthwhile to examine the properties of compounds of this latter type. Although such mixed anhydrides are known, their isolation has proved difficult and their reactions have received little study (8,9).

Scheme 1



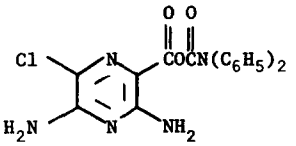
Reaction of the triethylamine salt of I with diphenylcarbamoyl chloride in DMF or DMSO produced a crystalline compound on dilution with water which was shown from its spectral and chemical properties and analysis, to be the desired mixed anhydride, IX. Like III, IX (10) is soluble in common organic solvents, and, surprisingly (8), it can be recrystallized from acetonitrile without decomposition. This unique compound has proven to be the most reactive and versatile acylating derivative of this series. Reaction with 3-amino-1,2,4-triazole and 2-aminobenzimidazole in refluxing tetrahydrofuran formed VIp and VIq while condensation with aniline produced VIe (yields >80%) at room temperature. Likewise, the products (VI) in Scheme 1 could be synthesized from IX under less strenuous conditions than necessary with

III. In general, condensation was complete within a few hours at room temperature.



VII

VIII



IX

As a result of this study, we have demonstrated the potential of acyloxyacrylamides and their vinylogous counterparts, the carboxylic-carbamic mixed anhydrides, as highly effective and generally applicable acylating species. These "active esters" react under extremely mild conditions yet are capable of isolation and rigorous purification.

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10. We are investigating extensions of this rare species, especially with other carboxylic acids. Although there is a structural similarity between I and anthranilic acids, the amino groups in I are non-basic and essentially non-nucleophilic.