Activation of α-Carbons of Amides

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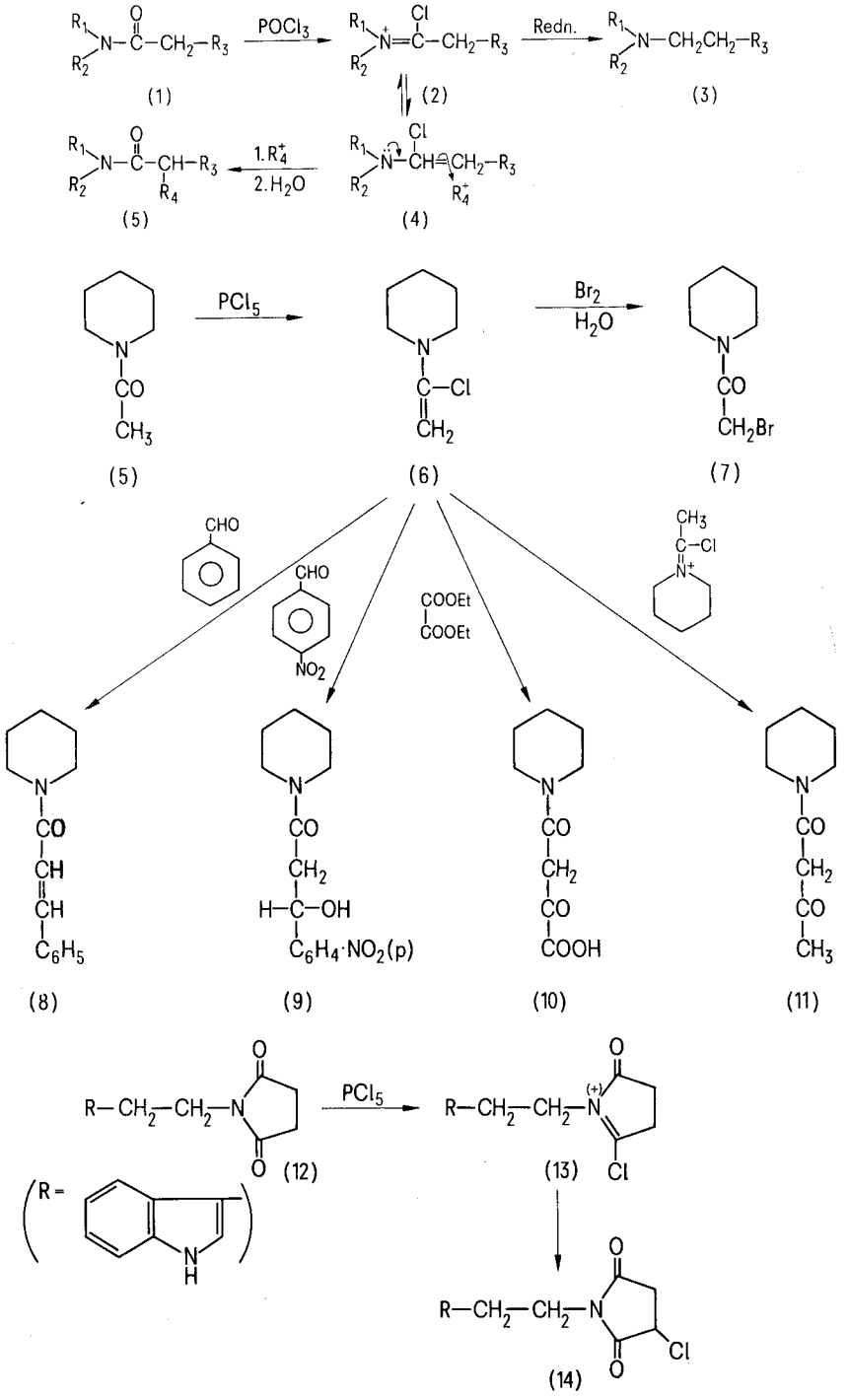
Summary. The reactions of Vilsmeir complexes of amides/imides with electrophiles afford the corresponding α-substituted products in good yield.

We have recently described new methods[1,2] for the reduction of amides (1) to amines (3) by generating Vilsmeier complexes (2) of amides which are readily reducible in high yields with sodium borohydride[1] or zinc/ethanol[2]. Since these immonium complexes can exist in tautomeric equilibrium with their enamine forms (2 ⇌ 4) enamine reactions at the carbon atom β to the nitrogen atom with various electrophilic reagents appeared as an attractive method for the functionalization at the carbon atom α to the amide carbonyl groups.



The procedure generally employed to affect such functionalizations[3–10] suffer from the drawback that they employ strong bases to generate anions prior to reaction with electrophiles. The presence of esters, ketones, aldehydes, etc., in the same molecules would result in preferential attack at the carbon atoms α to these more electrophilic carbonyl groups. BAN et al.[11,12] have developed an alternative procedure involving the use of MEERWEIN reagent[13–15] to generate the enaminoether of the amide which can then be alkylated. This reagent, however, alkylates alcohols, phenols, carboxylic acids, amines[13,14]. More recently, observation of intermolecular condensation reactions of Vilsmeier complexes by attack of the enamine on the immonium intermediates have been made, but attempts to use these as synthetically useful reactions for functionalization of amides have met with very limited success[16].

We now report substitution reactions in high yield at carbon atoms α to amide and imide carbonyl groups. The method employed involves the prior formation of the Vilsmeier intermediate of the amide (or imide) with phosphorus pentachloride in an aprotic solvent. This complex is then allowed to react with a suitable electrophile for a few hours to afford the desired functionalized amide on aqueous work-up.

Thus *N*-acetyl piperidine (5) was treated with phosphorus pentachloride in warm benzene for 10 min to afford the corresponding chloroenamine (6). To this was then added an equivalent amount of bromine in dioxane and the mixture was stirred at 30° for 4 h. On aqueous work-up, the product (7) was isolated as a white crystalline material in 80% yield, m.p. 38–40 °C.

Similarly, when the Vilsmeier intermediate (6) was allowed to react with an equivalent amount of benzaldehyde or *p*-nitrobenzaldehyde for 4 h in refluxing benzene, (8) and (9) were obtained in 80 and 90% yield respectively.

Treatment of the Vilsmeier complex (6) with diethyloxalate in refluxing benzene for $1^1/_2$ h afforded the corresponding acetylated acid (10) in 45% yield on aqueous work-up.

When alkylation was attempted with epichlorohydrin, the Vilsmeier complex (6) afforded only the intermolecular acylation product (11) in 60% yields.

In order to examine the possibility of similar activation of imide carbonyls, the imide (12) was treated with excess phosphorus pentachloride in benzene for 4 h when complete conversion to a new faster moving substance was detected by TLC. Aqueous work-up, extraction with ethyl acetate and concentration afforded colourless crystals, m.p. 169–71°. The IR-spectrum showed peaks at 1710 cm^{-1} (S) and 1790 cm^{-1} (W). The UV-spectrum afforded maxima at 224, 274 and 291 nm in expectation with the normal indolic chromophore. The mass spectrum afforded a prominent molecular ion at 276 with the isotope peak of chlorine at 278. Other major peaks appeared at 115, 116, 130, 114, 164, 177, 241 and 258 nm. Structure (14) was therefore assigned to the product.

In view of these reactions, it appears that this procedure for activating amides and imides may be significantly superior to the methods previously described, both in its scope as well as selective applicability. Extension of this method to other reactions involving both attack of various nucleophiles at the activated carbonyl groups and attack of other electrophiles at α-carbon atoms is currently being investigated.

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Ambivalent Effect of Protein Binding on Computed Distributions of Metal Ions Complexed by Ligands in Blood Plasma

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Summary. Although the absolute concentrations of metal complexes in blood plasma are controlled by protein binding, the percentage distribution of transition metal ions amongst low molecular weight ligands is not. Thus, computer simulations which omit protein equilibria can nevertheless afford reliable information about such metals in the biofluid.

Although the vast majority of transition metal ions in blood plasma are protein bound, low molecular weight complexes play an essential physiological role[2–4]. In particular, they may alter the bioavailability of the metal by mediating in its exchange between macromolecules[5,6] and also by facilitating membrane penetration[7–10]. Moreover, the free aquo-ions of metals such as Fe(III) and probably Cu(II) exist in plasma at such low concentrations that it is extremely unlikely that they, rather than their low molecular weight complexes, participate in bioinorganic reactions. The nature and relative concentrations of these complexes are thus of considerable interest.

Current analytical methods are incapable of measuring individual concentrations of low molecular weight complexes in plasma. This is due to the multicomponent nature of the system as well as to their extremely low concentrations. Further, the complexing reactions are