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Synthetic Studies on N-Acetyl Derivatives of Amino Acids and Thiolactone using Vilsmeier-Haack Reagent

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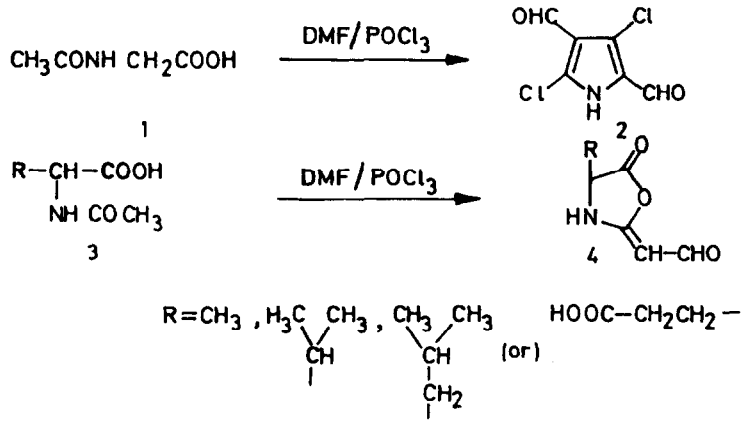
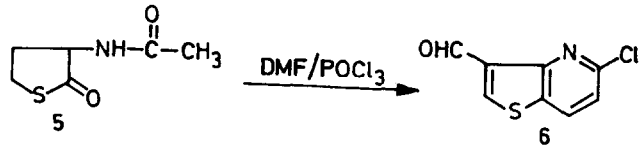
Abstract: A variety of N-acetyl derivatives of amino acids have been subjected to Vilsmeier reagent to obtain 2,4-dichloro-3,5-diformylpyrrole and 2-formylmethylene-4-substituted oxazolidin-5-ones. The N-acetyl homo cysteine thiolactone gave 5-chloro-3-formylthieno (2,3-b)pyridine on reaction with Vilsmeier reagent.

Amino acids[1] form an important class of substances of considerable biological interest. They are components of growing list of important antibiotics. These compounds serve for the construction of peptide analogues and also serve as synthons to lactams and other useful compounds. Pyrrole derivatives form one of the most important biologically active compounds. The five membered ring system of pyrrole is one of the most ubiquitous throughout the plant and animal kingdom because of its involvement as a subunit of haem and the chlorophylls. The introduction of substitutents into the β-position of pyrrole is of current interest in view of the importance of this class of compounds in natural product synthesis and more recently in the application of pyrrole compounds in the synthesis of organic metals[2].

On the basis of above findings and in continuation of our interest on the Vilsmeier reagent [3-5], we focused our attention to convert some N-acetyl amino acids into pyrrole derivatives via Vilsmeier reagent ($DMF/POCl_3$). The N-acetyl glycine (**1**) on reaction with Vilsmeier reagent at 90°C led to the formation of diformylated product namely 2,4- dichloro-3,5-diformylpyrrole (**2**) in good yield (82%). As N-acetyl glycine gave a diformyl pyrrole, a variety of N-acetyl amino acids like alanine, valine, leucine, and glutamic acids (**3**) have been subjected to Vilsmeier reagent at 80-90°C but all these compounds gave monoformylated products namely 2-formylmethylene-4-substituted oxazolidin-5-ones (**4**) in 30-38% yields. When the reaction was carried out at 60°C, only starting material was recovered, when the reaction was carried out at 100°C only a viscous uncharacterisable material was obtained.



Vilsmeier reactions on lactonic Carbonyl compounds have not been widely studied[6]. This prompted us to study the reaction further using N-acetyl homo cysteine thiolactone (**5**).



The thiolactone on reaction with Vilsmeier reagent at 90°C led to the formation of 5-chloro-3-formyl-thieno[2,3-b]pyridine (**6**) in reasonably good yield (60%). It is interesting to note that during the course of the reaction, formylation occured both at methyl group leading to cyclization and also in the thiophene ring.

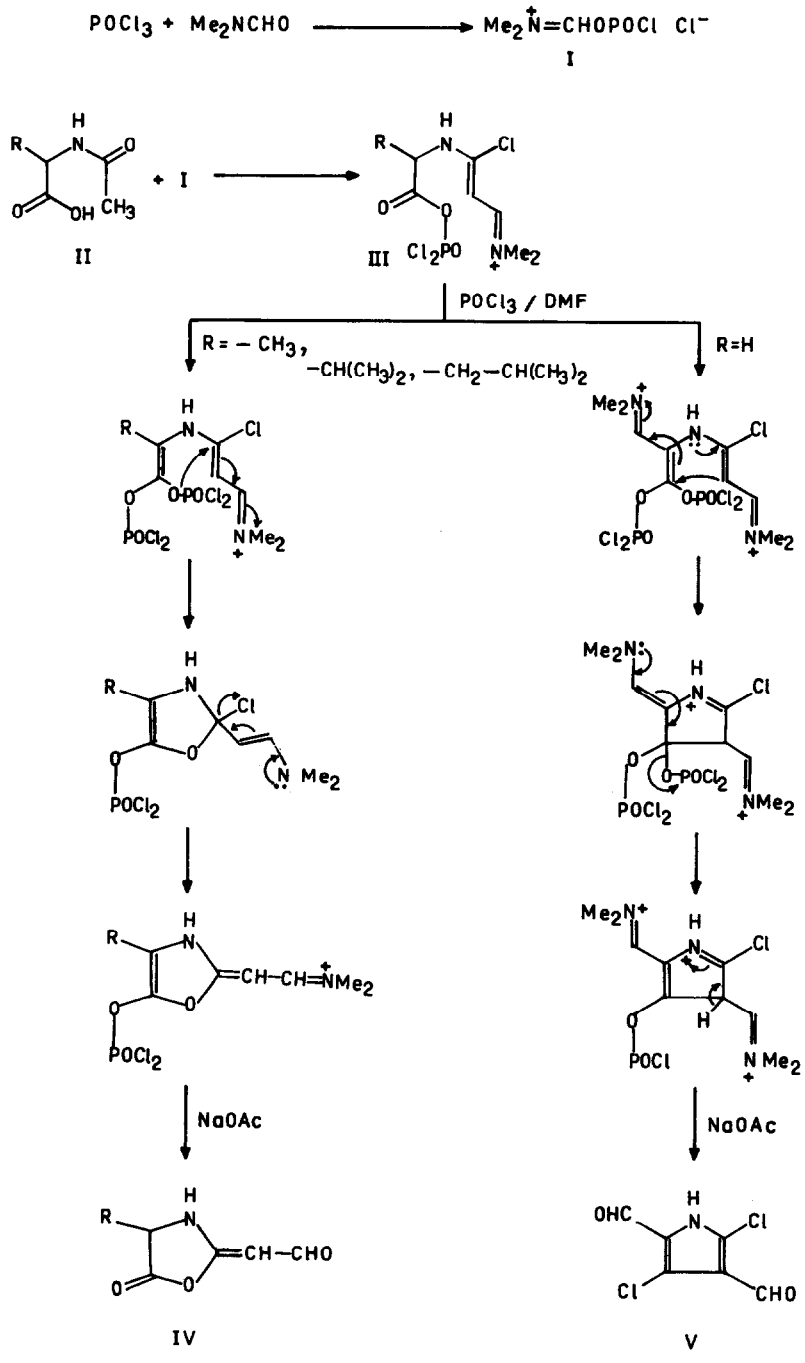
All the compounds were characterised by IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analysis[7]. The results are summarised in Table 1.

Table 1: Reaction products of N-acetylamino acids and thiolactone **5** with $POCl_3$ and DMF.

Compound	m.p° C.	Yield[a] (%)
2	170	82
4a	124	36
4b	128	38
4c	132	35
4d	141	45
6	130	60

a All compounds gave satisfactory C & H analysis.

Scheme.1


POCl3 + Me2NCHO
Me2N+=CHOPOCl Cl−
I
II
III
+ I
POCl3 / DMF
R = − CH3, −CH(CH3)2, −CH2−CH(CH3)2
R=H
NaOAc
NaOAc
IV
V

While it would be premature to discuss the detailed mechanism of the above reaction at this stage, the general pattern of the reaction can be recognized. The scheme 2 shows a tentative mechanism for the formation of products. Phosphorus oxychloride reacts with N, N-dimethyl formamide to give a complex (I) which in turn undergoes electrophilic substitution reaction with the carbonyl moiety of N-acetyl derivative (II) to provide the chloromethyleminimum species (III). The complex (III) further undergoes reaction with the acid derivatives to give products depending upon the α-substitution. If groups like (R-CH_3, $(CH_3)_2$ CH, $(CH_3)_2$ CH-CH_2 etc.,) are present in III, the reaction leads to oxazolidinones (IV) whereas if R = H, in the complex (III) it undergoes diformylation to give the pyrrole derivative (V) as represented in scheme 1.

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7. Compounds **2** : ^{1}H NMR ($CDCl_3$): 9.66 (s, 1H, - C<u>H</u>O), 9.95 (s, 1H, - C<u>H</u>O); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): 180, 177, 118.31, 123.28, 128.83, 130.03, MS (m/e): 191 (M^+). 4b: ^{1}H NMR ($CDCl_3$): 9.6 (s, 1H, - C<u>H</u>O) 9.15 (s (broad), 1H, NH) 6.28 (s, 1H, = C<u>H</u>-C) 2.85 (m, 1H,-C<u>H</u>-) 1.4 (d, 1H-C<u>H</u>-N) 1.25 (s, 3H,- C<u>H</u>$_3$) 1.19 (s, 3H, - C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$): 21.8, 21.9, 27.0, 31.2, 102.6, 124.2, 165.2, 184.2; MS(m/e) : 169 (M^+). **6** : ^{1}H NMR ($CDCl_3$) : 7.54 (d, 1H, = C<u>H</u>) 8.0 (d, 1H = C<u>H</u>) 8.74 (s, 1H, = C<u>H</u>-S) 10.53 (s, 1H, -C<u>H</u>O); ^{13}C NMR ($CDCl_3$): 123.8. 124.6, 132.2, 132.8, 138.1, 150.6, 158.5, 189.9; MS(m/e) : 197 (M^+).

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