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Synthesis of 5-Chloropyrrole Carboxaldehydes from 5-Oxopyrrolidine Carboxamides.

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Abstract: N-alkyl-5-chloropyrrole-2(or 3)-carboxaldehydes are obtained by treatment of N-alkyl-5-oxopyrrolidine-2 (or 3)-carboxamides by phosphorus oxychloride and basic hydrolysis.
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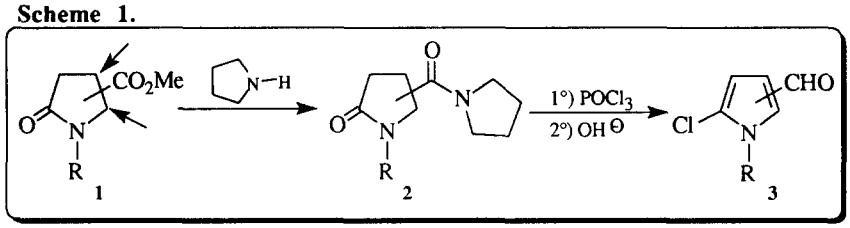
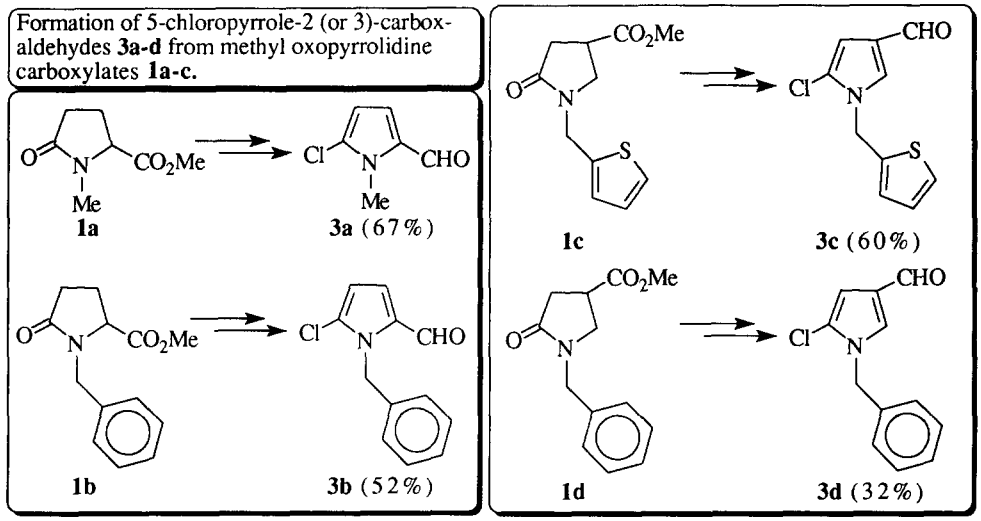
The general access of the pyrrole ring involved condensation of α-aminocarbonyl compounds with various synthons such as 1,3-dicarbonyl compounds, β-aminoenones, β-chlorovinylketones and 3-alkoxy-acroleins.[1] Recently, reduction of γ-nitroketones,[2] cyclization of thioimidates with Michael acceptors[3] and condensation of acetoxynitro compounds with isocyanoacetonitrile[4] have been described. However, only few syntheses reported convenient preparations of chloropyrrole carboxaldehydes. These compounds could be prepared using two main pathways: i) a Vilsmeier-Haack reaction on unstable chloropyrrole derivatives[5] or N-alkyl-pyrrolin-2-ones which are difficult to obtain,[6] ii) the chloration of formylpyrroles, which led to a mixture of mono and dichloro compounds.[7] More recently, N-alkyl-5-chloropyrrole-2-carboxaldehydes have been prepared in low to moderate yields by the action of the Vilsmeier-Haack reagent on succinamidals.[8] In the present paper (Scheme 1), we report a method for the preparation of N-alkyl-5-chloropyrrole-2(or 3)-carboxaldehydes from methyl oxopyrrolidine carboxylate derivatives.

Scheme 1.



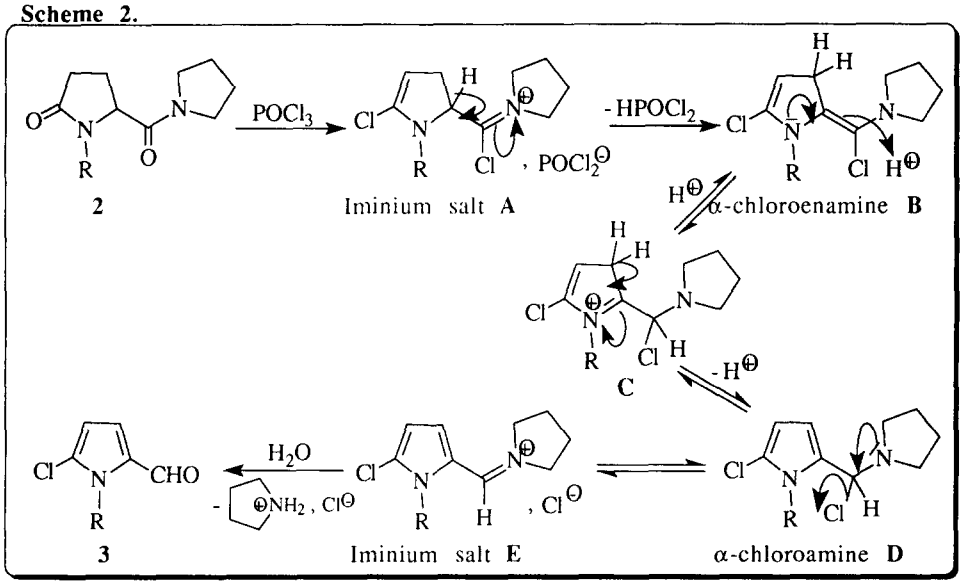
Thus, the typical reaction[9] starts by heating N-alkyloxopyrrolidine methyl esters **1** with pyrrolidine to lead quantitatively the bis-amides **2**. Treatment of the latter by phosphorus oxychloride followed by hydrolysis with sodium hydroxyde afforded a number of various N-substituted pyrroles **3** in moderate yields as shown in the following table.

*Fax (+33) 02-35-21-22-08



The structures of all intermediates **2a-d** and final products **3a-d** were confirmed by ^{1}H NMR spectroscopy and elemental analysis. Data for the known compounds have been compared with those reported in the literature.[10]

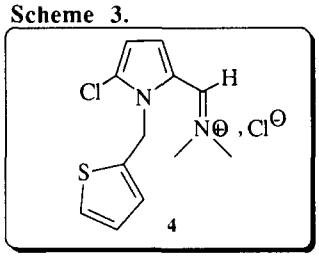
Scheme 2.



In the reaction described here, the carboxamide substituent in the presence of phosphorus oxychloride could appear as an *in situ* Vilsmeier-Haack reagent, so the aromatization of a saturated lactam was surprising. To our knowledge, pyrroles have been obtained only from unsaturated lactams, directly from pyrrolinones[11] or from succinamidals which led easily to such structures.[8] Taking into account that the chlorination of

pyrrolidinones is well known,[12] the reaction sequence listed in scheme 2 may be proposed as a mechanism of the formation of **3a** starting from the iminiun salt intermediate **A**. The reaction takes place through an α-chloro-enamine **B** by loss of one molecule of $HPOCl_2$. The protonation of the chloroenamine **B** by $HPOCl_2$ or by **A** led to the iminium ion **C**. The latter looses a proton to give the stabilized α-chloroamine **D**.[13] The carboxaldehyde **3** is obtained by elimination of the chloride ion followed by the hydrolysis of the iminiun intermediate **E**. Under these conditions, 5-oxoproline methyl ester (**1**, R=H) and 1-(thien-2'-ylmethyl)-5-oxoproline methyl ester (**1**, R = thien-2'-ylmethyl) led only to intractable tar, probably through a polymerization of the intermediate iminium salt **E** during the hydrolysis. To confirm this hypothesis, we have prepared the dimethyliminium salt **4**[14,15] isomer to **E** from the Vilsmeier-Haack formylation of 1-(thien-2'-ylmethyl)-succinamidal.[16] Whatever the conditions of hydrolysis, compound **4** (Scheme 3) appears unstable and did not give the expected 5-chloro-1-(thien-2'-ylmethyl)pyrrole-2-carboxaldehyde.

Scheme 3.



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In summary, a new, simple and efficient method for the synthesis of N-alkyl-5-chloropyrrole-2(or 3)-carboxaldehydes has been developped from readily available methyl N-alkyloxopyrrolidine carboxylates and cheap reagents. Further studies are in progress to investigate scope and limitations of this synthesis.

References and notes

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9. **Typical procedure:** A solution of methyl oxoprolinate derivative **1** (1 mmol) in 10 ml of pyrrolidine was refluxed for 3 hours. The excess of pyrrolidine was evaporated *in vacuo* and then, 10 ml of phosphorus oxychloride were added to the residue. The mixture was heated with stirring at 60°C for 3 hours. After cooling the dark solution was diluted with water (20 ml), made basic with 50% sodium hydroxyde solution and extracted with CH_2Cl_2. The organic layer was dried on $MgSO_4$ and concentrated to give **3** as a residue which was purified by liquid chromatography on silica gel column eluting with CH_2Cl_2.
10. **3a**: analytical data were identical to those in reference 5.

3b: analytical data were identical to those in reference 8.

Selected data for compound **3c**: mp 70°C; ^{1}H NMR ($CDCl_3$): δ 5.35 (s, 2H, CH_2-N), 6.43 (dd, J = 1.35 and 1.6 Hz, 1H, H_4), 6.95 (dd, J = 3.5, 5.1 Hz, 1H, $H_{4'}$), 7.05 (dd, J = 1.3 and 3.5 Hz, 1H, $H_{3'}$), 7.37 (dd, J = 1.3 and 5.1 Hz, 1H, $H_{5'}$), 7.71 (d, J = 1.6 Hz, 1H, H_2), 9.57 (d, J = 1.35 Hz, 1H, CHO); Anal. Calcd. for $C_{10}H_8ClNOS$ (225.69): C, 53.22; H, 3.57; N, 6.21. Found: C, 52.96; H, 3.51; N, 6.03.

Selected data for compound **3d**: mp 68°C; ^{1}H NMR ($CDCl_3$): δ 5.10 (s, 2H, CH_2-N), 6.56 (d, J = 1.8 Hz, 1H, H_4), 7.10-7.35 (m, 5H, 5H-benzene), 7.32 (d, J = 1.8 Hz, H_2), 9.62 (s, 1H, CHO); Anal. Calcd. for $C_{12}H_{10}ClNO$ (219.67): C, 65.61; H, 4.59; N, 6.38. Found: C, 65.71; H, 4.67; N, 6.32.

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15. Selected data for compound **4**: mp 172°C (decomp); ^{1}H NMR ($CDCl_3$): δ 3.23 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 5.37 (s, 2H, CH_2-N), 6.72-6.77 (m, 1H, H_4), 6.82-6.86 (m, 1H, $H_{4'}$), 7.04-7.11 (m, 2H, $H_{3'}$ and $H_{5'}$), 7.69-7.71 (m, 1H, H_2), 9.19 (s, 1H, CH=N); ^{13}C NMR ($CDCl_3$): δ 39 (CH_2), 40.3 (CH_3), 47.4 (CH_3), 102.1 (CH), 122.1 (CH), 124.8 (CH), 126.3 (CH), 126.5 (CH), 131.6 (C), 141.1 (C), 151.6 (CH), 168.6 (C), 179.1 (CH=N).
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