Direct Vilsmeier–Haack Chloroacetylation of Pyrroles

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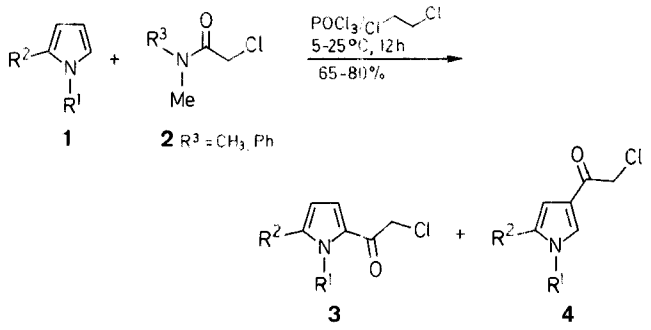
Reaction of pyrroles with *N,N*-dimethyl-2-chloroacetamide in the presence of phosphorus oxychloride leads to a mixture of 2- and 3-chloroacetylpyrroles, which can be separated by chromatography.

Electrophilic substitution in *N*-unsubstituted pyrroles occurs preferentially at the α-position.[1] This orientation is modified in *N*-substituted pyrroles and electrophilic substitution leads to a mixture of α- and β-derivatives.[2,3]

The 2- and 3-chloroacetylpyrroles are key intermediates in the synthesis of pharmacologically active compounds[4] and naturally occurring porphyrins.[5] As intermediate compounds related to our studies, we desired a direct method of synthesis of *N*-substituted 3-chloroacetylpyrroles. It is not possible to prepare compounds **4** by direct side chain halogenation[6] of the corresponding ketones, hence we have examined a modified Vilsmeier–Haack formylation method. We have now found that the reaction of *N*-substituted pyrroles **1** with *N,N*-disubstituted-chloroacetamides **2** in the presence of phosphorus oxychloride gives a mixture of 2- and 3-chloroacetyl derivatives **3** and **4** in good overall yields.



1 **2** $R^3 = CH_3$, Ph

3 **4**

1, 3, 4	R^1	R^2	1, 3, 4	R^1	R^2
a	H	H	**d**	CH_2CH_3	H
b	H	CH_3	**e**	CH_2Ph	H
c	CH_3	H	**f**	Ph	H

The reaction was carried out in two steps: formation of Vilsmeier–Haack reagent from phosphorus oxychloride and *N,N*-disubstituted chloroacetamide **2** in the absence of solvent; and electrophilic substitution on pyrrole derivatives. Generally formation of the Vilsmeier-Haack reagent required 6 hours, as determined by NMR monitoring, when it was complete a solution of **1** in 1,2-dichloroethane was added. The mixture was then stirred at room temperature for 12–16 hours and hydrolyzed by pouring into 30% aqueous sodium carbonate solution.

The results are summarized in the Table. The reaction represents a convenient synthetic approach to 3-chloroacetylpyrroles **4**, despite the formation of a mixture of α- and β-derivatives, as they are easily separated by column chromatography (see experimental). The structure of the new compounds was fully assigned on the basis of analytical and spectroscopic data. Experimental results confirm that in the absence of a substituent on pyrrole nitrogen atom the reaction gave only 2-substituted products **3** (entries 1 and 2, Table), whereas with *N*-substituted

Table. α- and β-Chloroacetylpyrroles **3** and **4** Prepared

Entry	Products 3 and 4	Yield[a] (%)	Ratio[b] 3/4	2-Substituted Compounds 3a–f		3-Substituted Compounds 4c–f		
				mp (°C)[c] or bp (°C)/mbar	Molecular Formula or Lit. mp (°C) or bp (°C)/mbar	mp (°C)[c,d] or bp (°C)/mbar	Molecular Formula	^{1}H-NMR ($CDCl_3$/TMS)[f,g] δ, J(Hz)
1	**a**	75	100/0	115–116	115[9]	–	–	–
2	**b**	65	100/0	114–115	C_7H_8ClNO[h] (157.5)	–	–	–
3	**c**	80	50/50	46–48	47[10]	69–70	C_7H_8ClNO (157.5)	3.77 (s, 3H, CH_3); 4.45 (s, 2H, CH_2); 6.55 (dd, 2H, J = 3, H-4, 5); 7.3 (m, 1H, H-2)
4	**d**	65	45/55	75/0.3	70/0.3[10]	70/0.3	$C_8H_{10}ClNO$ (171.5)	1.5 (t, 3H, J = 7, CH_3); 4.0 (q, 2H, J = 7, CH_3CH_2); 4.4 (s, 2H, CH_2); 6.6 (dd, 2H, J = 3, H-4, 5); 7.4 (m, 1H, H-2)
5	**e**	75	35/65	89–91	91[10]	74–76	$C_{13}H_{12}ClNO$ (233.5)	4.35 (s, 2H, NCH_2); 5.1 (s, 2H, $PhCH_2$); 6.6 (dd, 2H, J = 3, H-4, 5); 7.1–7.4 (m, H-2 + $5H_{arom}$)
6	**f**	65	50/50	43–45	46[10]	85–87	$C_{12}H_{10}ClNO$ (219.5)	4.5 (s, 2H, CH_2); 6.75 (d, 1H, J = 3, H-4); 7.0 (d, 1H, J = 3, H-5); 7.3 (s, $5H_{arom}$); 7.7 (m, 1H, H-2)
7	**c**	15	20/80[i]					
8	**e**	10	10/90[i]					
9	**f**	10	10/90[i]					

[a] Yield of pure, isolated product.
[b] Ratio estimated on separated isomers.
[c] Uncorrected, measured with a Büchi capillary melting point apparatus.
[d] Recrystallized from diisopropyl ether.
[e] Satisfactory microanalyses obtained: C ±0.25, H ±0.12, N ±0.15.
[f] Recorded on Varian XL-200 spectrometer.
[g] Chemical shift values of H-2, H-4, H-5 and coupling constants agree with those reported[7] for 3-acetyl and 3-methoxycarbonyl substituted pyrroles.
[h] calc. C 53.33 H 5.07 N 8.88
found 53.21 5.05 8.78
^{1}H-NMR ($CDCl_3$/TMS): δ = 2.4 (s, 3H, CH_3); 4.5 (s, 2H, CH_2); 6.0 (d, 1H, J = 3 Hz, H-4); 6.9 (d, 1H, J = 3 Hz, H-3); 10.5 (s, 1H, NH).
[i] Reaction carried out with *N*-methyl-*N*-phenylchloroacetamide (**2**, R^3 = Ph).

pyrroles a mixture of α- and β-derivatives **3** and **4** was always obtained in about 1:1 ratio (entries 2–6).

The nature of the nitrogen substituents of the chloroacetamide **2** (R^3 = Me, Ph) also affects the product ratio of **3** to **4**. The presence of a phenyl instead of a methyl group turns the electrophilic substitution towards the β-position (ratio **3/4** = 1:9) (entries 7–9), probably due to steric hindrance in the transition state. Unfortunately in this case yields were very low as the Vilsmeier–Haack complex was difficult to form and monitoring the reaction with ^{1}H-NMR spectroscopy for 24 h revealed the presence of a large amount of unreacted chloroacetamide **2** (R^3 = Ph).

Chloroacetylation of Pyrroles; General Procedure:
N,N-Dimethyl-chloroacetamide[11] or *N*-methyl-*N*-phenyl-chloroacetamiden (22 mmol) is added to $POCl_3$ (6.1 g, 40 mmol) cooled to 5°C. The mixture is stirred at r.t. for 6 h until the formation of the complex is complete and then cooled to 5°C. A solution of the appropriate pyrrole **1** (20 mmol) in 1,2-dichloroethane (25 mL) is added, and the mixture is stirred at r.t. for 12–16 h under an N_2 atmosphere. The mixture is poured into 30% aq. Na_2CO_3 solution (100 mL). After stirring for 30 min, the mixture is extracted with CH_2Cl_2 (3 × 25 mL) and the solvent is evaporated to give the crude products.

In the case of *N*-unsubstituted pyrroles (entries 1 and 2) crystallization from diisopropyl ether gives **3a**; and the unknown 2-chloroacetyl-5-methylpyrrole (**3b**) mp 114–115°C (Table).

In the case of *N*-substituted pyrroles (entries 3–6) the residue is chromatographed on silica gel (60 g) using a mixture of toluene/EtOAc (9:1); as eluent to separate the mixture of 2- and 3-chloroacetyl derivatives **3** and **4** (R_f = 0.41 and 0.29, respectively, toluene/EtOAc (9:1) (Table).

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