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Unexpected Formation of Acylformamidines by Reaction of Primary Carboxamides with MeONa in DMF in the Presence of $CHCl_3$

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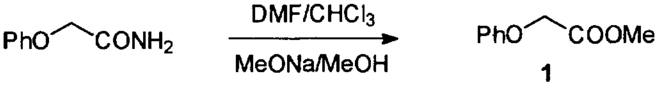
Abstract: Dichlorocarbene, which is generated by reaction of $CHCl_3$ with MeONa, is likely to chlorinate DMF to produce the Vilsmeier-Haack-Arnold salt that, in the presence of excess MeONa, gives DMF dimethylacetal (**2**). This latter reacts with primary amides to yield the corresponding *N,N*-dimethyl-*N'*-acylformamidines. Solid state structure of *N*-[(dimethylamino)methylene]phenoxyacetamide (**4**) obtained by X-ray crystallography is also reported. © 1997 Elsevier Science Ltd.

In the synthesis of X-ray contrast agents *via* Smiles rearrangement of 3,5-disubstituted 2,4,6-triiodophenoxyacetamides,[1] apart from the expected *N*-(hydroxyacetyl)anilines, we also isolated the methyl esters deriving from the starting primary amides when working in the presence of $CHCl_3$.[2] In order to avoid Smiles rearrangement, the reaction was tested on a non iodinated substrate such as phenoxyacetamide and we observed its conversion into methyl phenoxyacetate (**1**). (Scheme 1). It was immediately clear that the reagent responsible for the reaction was related to $CHCl_3$ because, performing the rearrangement in the absence of $CHCl_3$, **1** was not formed. We decided to investigate the mechanism of such unusual transformation.



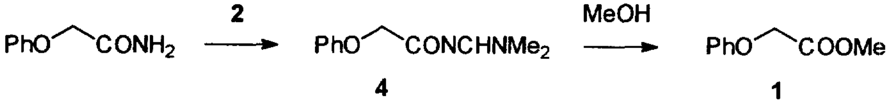
Scheme 1

The two major products generated by reaction of $CHCl_3$ and DMF in the presence of either solid MeONa or MeONa in MeOH (see Experimental) were isolated and identified as dimethylformamide dimethylacetal (**2**) and trimethyl orthoformate (**3**).[3] (Scheme 2).

$$CHCl_3 \xrightarrow[\text{MeONa(MeOH)}]{\text{DMF}} \underset{\mathbf{2}}{(MeO)_2CHNMe_2} + \underset{\mathbf{3}}{HC(OMe)_3}$$

Scheme 2

The conversion depicted in Scheme 1 can be explained through the intermediacy of a compound, generated by reaction of phenoxyacetamide with **2**[8], which was isolated in 56% yield and proved to be *N*-[(dimethylamino)methylene]phenoxyacetamide (**4**). This is in accord with the results of Lin *et al.*[9] even though these authors obtained acylformamidines by reaction of primary amides in refluxing **2**. The reactivity shown by phenoxyacetamide to give **4** was also observed with other substrates. Indeed, benzamide and nicotinamide treated with $CHCl_3$ and MeONa in DMF gave the corresponding acylformamidines in 65 and 55% yields, respectively. As a further step in the elucidation of the reaction mechanism we found that, when dissolved in MeOH, **4** affords **1** in high yields. (Scheme 3). This finding has led to the development of a new procedure for the reaction of primary amides with **2** in the presence of the suitable alcohol to give the corresponding carboxylic ester.[10]



Scheme 3

Solid state structure of 4

Figure 1 reports the ORTEP view. The crystal packing is made up by $C_{11}H_{14}N_2O_2$ molecules. There are two significant features shown by the structure: *i*) the "*all trans*" conformation adopted by the torsion angles of the side chain; *ii*) the overall planar arrangement of the molecule. In this respect, the sp^2 character of N2 is also evidenced both by the notably short C9-N2 distance (1.317(2) Å), which is comparable with that of the N1-C9 linkage (1.309(2) Å), and by the sum of the angles around N2 (360°). As a consequence of the extended conjugation interesting the O2-C8-N1-C9-N2 fragment also the C10, C11 and C7 atoms are on the conjugation plane. On the other hand, the partial double bond character of the O1-C1 bond (1.362(2) Å, C1-O1-C7 117.8(1)°) forces the C7 atom to lie in the same plane of the phenyl ring. Finally the H9 hydrogen atom is interested in both intramolecular and intermolecular hydrogen bonds with the O2 oxygen atom: C9-H9···O2 2.270(3) Å and C9-H9···O2 (-x,-y,1-z) 2.493(2) Å.

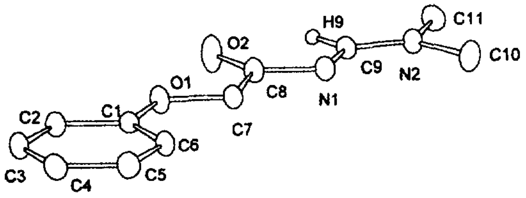
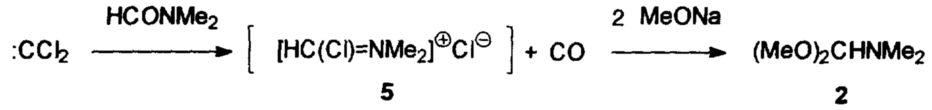


Figure 1. Solid state structure of acylformamidine **4** obtained by X-ray crystallography

Mechanism of formation of acetal 2

The most puzzling step is the formation of **2** from $CHCl_3$ and DMF in the presence of MeONa. To the best of our knowledge such reaction has never been reported. Acetal **2** could be formed by reaction of $:CCl_2$ with dimethylamine, possibly deriving from the decomposition of DMF.[11] However, only traces (< 1%) of $HNMe_2$ with respect to MeONa were found in a mixture devoid of $CHCl_3$ thus precluding the possibility of such a path to explain the formation of large amounts of **2**. Some scattered references[13] describe that $:CCl_2$ can convert alcohols into the corresponding alkyl chlorides. Accordingly, we believe that, in the present case, $:CCl_2$ acts as a chlorinating agent on the enolic form of DMF to give the chloromethyleniminium salt (Vilsmeier-

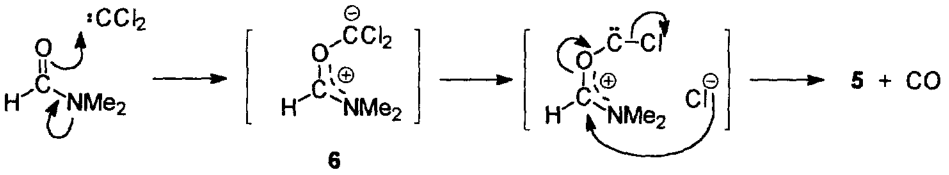
Haack-Arnold chloride, 5)[14] **that subsequently reacts with sodium methoxide to afford 2.**[12,15] **(Scheme 4). The detection of CO as the gas evolving from the mixture supports such path for the formation of 2.**



$$:CCl_2 \xrightarrow{HCONMe_2} \left[\ \underset{\mathbf{5}}{[HC(Cl){=}NMe_2]^{\oplus}Cl^{\ominus}}\ \right] + CO \xrightarrow{2\ MeONa} \underset{\mathbf{2}}{(MeO)_2CHNMe_2}$$

Scheme 4

We have taken into account the possibility that $:CCl_2$ could chlorinate[13] MeOH to give MeCl and CO. However, in the case of reactions carried out with solid MeONa, it was possible to quantitate MeOH (see Experimental). We found that the amount of MeOH present in the reaction mixtures is close to that expected for the formation of **2** and **3** and this indicates that the chlorination, if occurring at all, is negligeable. The preferential reaction of DMF rather than MeOH can find explanation in that DMF is a substrate particularly prone to chlorination by a variety of reactants such as $SOCl_2$, $COCl_2$, PCl_5, $(COCl)_2$.[12,16] Furthermore, DMF has been used as catalyst in the chlorination of alcohols[17] through the intermediacy of **5**.[18] This latter species, as soon as it is formed, likely reacts with MeONa to give acetal **2** under our conditions. We believe that the conversion of DMF into **5** occurs according to the mechanism depicted in Scheme 5. Attack of the enolic form of DMF leads to the labile species **6** which undergoes α-elimination to generate **5**. Similar α-elimination has been invoked to explain the formation of **3** by reaction of MeONa with $:CCl_2$.[6]



Scheme 5

In conclusion we found that: *i*) acetal **2** is easily formed by reaction of $CHCl_3$ and MeONa in DMF; *ii*) the reaction of primary amides with $CHCl_3$ and MeONa in DMF affords acylformamidines even under mild conditions.[9]

EXPERIMENTAL

All solvents, obtained from commercial sources, were used without further purifications. Freshly opened DMF (Merck KGaA, Darmstadt, Germany; art. 10983) with a water content < 0.05%, was used. MeONa was prepared by dissolution of sodium in MeOH and either evaporated to dryness or diluted to afford a 2 M solution. ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded in DMSO-d_6. Elemental analyses were carried out at the Redox Laboratories (Cologno Monzese, Milan, Italy).

TLC quantitation of dimethylamine in DMF. (Merck KGaA silica gel plates $60F_{254}$; eluent: EtOAc/AcOH/H_2O = 3/2/2; detection: ninhydrin or Cl_2 + *o*-tolidine). In a vial equipped with screw cap, solid MeONa (0.27 g; 5 mmol) was added to DMF (5.5 ml) and the suspension was stirred for 30 min at 35 °C. After filtration under pressure (Millex®-HV 0.45 μm Millipore®) an aliquot was diluted with the same volume of 0.1 M HCl and the solution was used for TLC quantitation of dimethylamine hydrochloride. A content < 1% of the amine theoretically deriving from saponification of 5 mmol DMF was found.

Reaction of $CHCl_3$ and DMF in the presence of either solid MeONa (a) or MeONa in MeOH (b). First trials were performed using 3 molar equiv. of MeONa with respect to $CHCl_3$ as suggested by the stoichiometry of formation of **2** and **3**. Such conditions left 29% of unreacted $CHCl_3$ probably due to partial hydrolysis of MeONa by moisture present in DMF. We tentatively found that, under these experimental conditions (*vide infra*), 2 further molar equiv. of MeONa were required to completely consume $CHCl_3$.

(a): In a reaction flask (25 ml) protected from moisture ($CaCl_2$) solid MeONa (0.27 g; 5 mmol) was suspended in DMF (4.5 ml) at room temperature. A 1 M solution of $CHCl_3$ in DMF (1 ml) was dropped, over 1 min, into the vigorously stirred suspension. The exothermic reaction raised the temperature to 36 °C. After 30 min the reaction mixture was quickly poured into a volumetric flask (10 ml). Before diluting with DMF, *n*-nonane (30 μl, internal standard) was added. An aliquot was filtered (Millex®-HV 0.45 μm Millipore®) and analyzed by GC. **(b):** The experiment was run as described for **(a)** using a 2M solution of MeONa in MeOH instead of solid MeONa.

GC quantitations of the reaction components: **2**, **3** and $CHCl_3$ were quantitated using calibration curves obtained from GC analyses (DB5 J & W Scientific® 0.25 μm, 60 m x 320 μm column) performed with DMF solutions of authentic samples in the presence of *n*-nonane. Results as the average of three experiments: **(a):** $CHCl_3$ was converted into **2** (91%) and **3** (6%). **(b):** $CHCl_3$ was converted into **2** (48%) and **3** (38%). Under both reaction conditions $CHCl_3$ is completely consumed and small amounts of unknown side products are formed. For reactions under conditions **(a)** GC quantitation of MeOH was also performed: 97 ± 5% of the expected MeOH is present in the reaction mixtures.

***N*-[(Dimethylamino)methylene]phenoxyacetamide (4).** Into a suspension obtained by addition of MeONa (20.8 g, 385 mmol) to a solution of phenoxyacetamide (4 g, 26.5 mmol) in DMF (150 ml) a 3 M solution of $CHCl_3$ in DMF (35 ml, 105 mmol) was dropped in 20 min. The temperature raised to 37 °C and a brisk evolution of gas (CO as demonstrated by absorption through a CH 20601 Drager® tube) was observed. The reaction was monitored by HPLC. After 16 h the filtered solution was evaporated and the residue was treated with *n*-hexane (3x25 ml), then the solid was filtered and taken up in boiling Et_2O (120 ml). The hot cloudy solution was filtered from a brown tar and concentrated to 60 ml to obtain a crystalline solid. A further crystallization from Et_2O (70 ml) afforded **4** (3.1 g, 56%) as a white solid, mp 98-99 °C (uncorr.). ^1H NMR: δ = 2.99 (3H, s), 3.12 (3H, s), 4.68 (2H, s), 6.63-6.94 (3H, m), 7.26-7.30 (2H, m), 8.50 (1H, s); ^{13}C NMR: δ = 34.9 and 40.7 (CH_3), 68.8 (CH_2), 114.4 ($C_{Ar}2$ and $C_{Ar}6$), 120.4 ($C_{Ar}4$), 129.3 ($C_{Ar}3$ and $C_{Ar}5$), 158.3 ($C_{Ar}1$), 160.1 (CH), 179.5 (CO); $ESI^{(+)}$ MS: *m/z* 207 $[M + H]^+$, 229 $[M + Na]^+$. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.20; H, 6.89; N, 13.58.

***N*-[(Dimethylamino)methylene]benzamide.** Prepared in 65% yield as described for **4**. mp 74-75 °C (uncorr.) (*n*-hexane) lit.[9] 73-75 °C. ^1H NMR: δ = 3.11 (3H, s), 3.15 (3H, s), 7.42-7.53 (3H, m), 8.20-8.24 (3H, m), 8.64 (1H, s); ^{13}C NMR: δ = 34.8 and 40.8 (CH_3), 128.0 and 129.3 ($C_{Ar}2$ and $C_{Ar}3$), 131.6 ($C_{Ar}4$), 137.0 ($C_{Ar}1$), 160.8 (CH), 175.9 (CO); $ESI^{(+)}$ MS: *m/z* 177 $[M + H]^+$, 199 $[M + Na]^+$. Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.94; H, 7.02; N, 15.69.

***N*-[(Dimethylamino)methylene]pyridine-3-carboxamide.** Prepared in 55% yield as described for **4**. mp 61-63 °C (uncorr.) (*n*-hexane) lit.[9] 64-66 °C. ^1H NMR: δ = 3.13 (3H, s), 3.19 (3H, s), 7.42-7.49 (1H, m), 8.36-

8.43 (1H, m), 8.65-8.71 (2H, m), 9.29-9.30 (1H, m); ^{13}C NMR: $\delta = 35.0$ and 41.0 (CH_3), 123.3 ($C_{Ar}5$), 132.2 ($C_{Ar}3$), 136.5 ($C_{Ar}4$), 150.6 and 152.1 ($C_{Ar}2$ and $C_{Ar}6$), 160.9 (CH), 174.5 (CO); ESI$^{(+)}$ MS: *m/z* 178 $[M + H]^+$, 200 $[M + Na]^+$. Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.89; H, 6.20; N, 23.45.

Crystal Structure Determination of 4: A single crystal of **4** of appropriate size (0.6x0.5x0.3 mm) was mounted on a Enraf-Nonius CAD4 automatic diffractometer. Determination of the cell parameters was performed by least-squares refinement of 25 reflections. The compound crystallizes in the triclinic system, space group $P\bar{1}$, with a = 5.149(1), b = 9,947(3), c = 10.945(2) Å, $\alpha = 76.73(2)$, $\beta = 79.84(2)$, $\gamma = 89.72(2)°$; Z = 2; U = 536.7(2) Å^3; $\mu = 7.27$ cm^{-1}; $D_C = 1.28$ g cm^{-1}. 2032 Reflections were collected in the range $4<2\theta<70°$, using Cu-Kα radiation ($\lambda = 1.5418$ Å, graphite monochromated), θ-2θ scan mode, and successively corrected for Lorentz and polarization effects. An absorption correction was applied, using the Walker and Stuart method,[19] once the structure was solved. The direct methods of SIR92[20] were used to solve the structure, which was then refined by the full-matrix least-squares technique of SHELXL-93[21] to R = 0.074 and wR2 = 0.21 using the 1880 reflections having $I>2\sigma(I)$. All the non-hydrogen atoms were refined anisotropically, whereas the hydrogen ones were introduced in calculated positions with their positions refined according to the linked atoms and treated isotropically. A total of 139 parameters were refined. The final overall temperature factor of the hydrogen atoms was 0.073 Å^2. Tables 1 and 2 collect selected bond distances and angles, respectively. Atomic scattering factors were taken from ref. 22. Geometrical calculations were performed by PART93[23] and the molecular plots were produced by the ORTEP program.[24]

Table 1. Bond Lengths [Å] for **4**.

O(1)-C(1)	1.362(2)	C(7)-C(8)	1.512(3)
O(1)-C(7)	1.416(2)	C(8)-O(2)	1.217(2)
C(1)-C(6)	1.390(3)	C(8)-N(1)	1.384(2)
C(1)-C(2)	1.395(3)	N(1)-C(9)	1.309(2)
C(2)-C(3)	1.371(3)	C(9)-N(2)	1.317(2)
C(3)-C(4)	1.388(3)	N(2)-C(10)	1.450(3)
C(4)-C(5)	1.382(3)	N(2)-C(11)	1.452(3)
C(5)-C(6)	1.383(3)		

Table 2. Angles [deg] for **4**.

C(1)-O(1)-C(7)	117.78(14)	O(1)-C(7)-C(8)	108.7(2)
O(1)-C(1)-C(6)	125.2(2)	O(2)-C(8)-N(1)	127.0(2)
O(1)-C(1)-C(2)	115.3(2)	O(2)-C(8)-C(7)	121.5(2)
C(6)-C(1)-C(2)	119.5(2)	N(1)-C(8)-C(7)	111.5(2)
C(3)-C(2)-C(1)	120.1(2)	C(9)-N(1)-C(8)	113.4(2)
C(2)-C(3)-C(4)	120.7(2)	N(1)-C(9)-N(2)	124.0(2)
C(5)-C(4)-C(3)	119.1(2)	C(9)-N(2)-C(10)	122.0(2)
C(4)-C(5)-C(6)	120.8(2)	C(9)-N(2)-C(11)	121.6(2)
C(5)-C(6)-C(1)	119.7(2)	C(10)-N(2)-C(11)	116.4(2)

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