

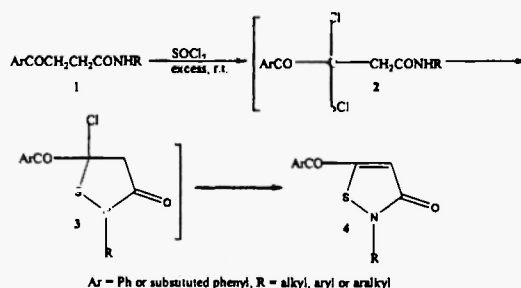
A CONVENIENT ONE-POT SYNTHESIS OF α -CHLORO- α -CHLOROSULFENYL-IMIDOYL CHLORIDES *via* AN ABNORMAL REACTION OF EXCESS THIONYL CHLORIDE ON SECONDARY AMIDES

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Abstract : A one-pot procedure is described for the preparation of α -chloro- α -chlorosulfenyl-imidoyl chlorides from the abnormal reaction of thionyl chloride on some secondary amides. The results are consistent only with excess thionyl chloride oxidation proceeding exclusively at the α -methylene to the amide carbonyl function. The functionality of these products plus the efficiency of the method and the good yields, (up to 75 %), could offer a useful tool for synthetic purposes.

The abnormal reactions of thionyl chloride, which are known for a long time, all involve oxidation of aliphatic carbon atoms and can be classified as follows. (a) Methyl carbons adjacent to aromatic rings, (phenyls¹ or heteroaromatics^{2,3}), resulting to the corresponding carboxylic acids, while sulfur dichloride in some instances was reported, as by-product. (b) Methylene carbons adjacent to an aryl group and a carboxylic group, which are converted to the corresponding α -chloro- α -chlorosulfenyl-carboxylic acid chlorides. The authors⁴ suggest a mechanism involving oxidation of benzylic position, this is the first literature report of formation of a sulfenyl chloride by this reagent. (c) Methylene carbons adjacent to a carbonyl group (ketonic or carboxylic), including the methine carbon of cinnamic acids, *alpha* to the carbonyl moiety. Definitive evidences that oxidations with thionyl chloride, (usually in the presence of pyridine),⁶ occur at the α -carbon atom to the carbonyl function rather than at a benzylic position (e.g. arylpropionic acids and 4-aryl-2-butanones), were presented in a series of interesting papers^{3a-g}. Moreover in some cases the α -chloro- α -chlorosulfenyl derivatives were separated and used for further reaction^{5g} to sulfur heterocycles (e.g. benzo[b]-thiophenes). The authors suggested also a mechanism in terms of a Hell-Vohlard-Zelinsky type where addition of thionyl chloride to the enol of a ketone or of a carboxylic acid chloride or to a cinnamoyl chloride carbon-carbon double bond, affords an α -sulfinyl chloride which may be converted to the sulfenyl chloride by a sequence that bears close analogy to the established mechanism of the Pummerer reaction. (d) Active methylenes as of that of arylacetonitriles have been reported⁷ to be converted to the corresponding α -chloro- α -chlorosulfenyl derivatives in presence of gaseous hydrogen chloride. The conversion of other active methylenes as of that of diethyl malonate, benzyl phenyl ketone, phenylacetic acid, propiophenone and propionic acid's methylene but not α -methylenes of monocarboxylic esters to the α -chloro- α -chlorosulfenyls, (in the presence of pyridine), and then the conversion of this moiety into carbonyl group through the sulfenamides prepared by treating the former with primary amines have been reported.⁸ The oxidative conversion of a series of β -arylpropionamides **1** to 5-aryl-3(2H)-isothiazolones **4**, using a large excess of thionyl chloride, (without any base) was reported⁹ some years ago. The key to the mechanism of formation of these heterocycles was the intermediacy of sulfenyl chloride **2** by oxidation of the methylene adjacent to the ketonic carbonyl function, undergoing cyclization *via* a nucleophilic displacement of the amide nitrogen on sulfenyl chloride group, and elimination of hydrogen chloride from **3** (Scheme 1).

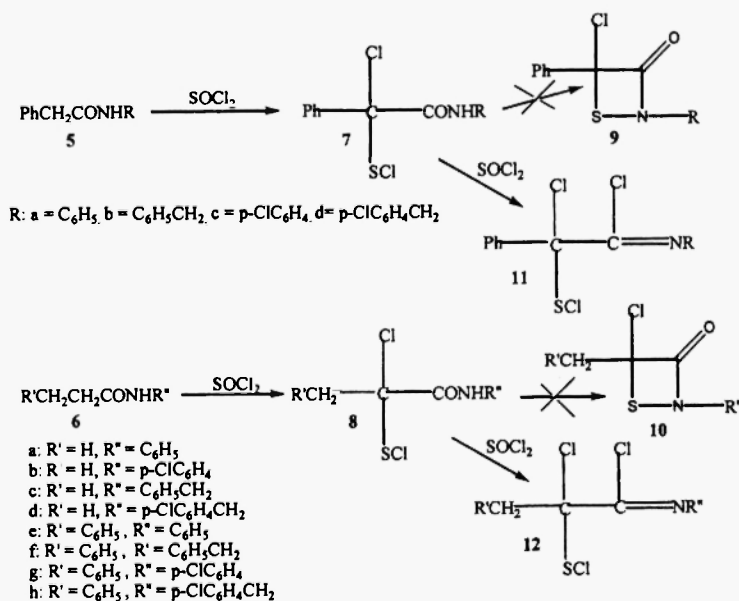


Scheme-1

These reports⁹ prompted us to study the oxidative behavior of thionyl chloride on some amides¹⁻¹⁰ phenylacetic, propionic and β -phenylpropionic acids **5** and **6**. The formation of 1,2-thiazetidii

9 and 10 was excluded and instead the unusual nature products, the α -chlorosulfenyl chlorides-imidoyl chlorides 11 and 12, were obtained, rather through the corresponding sulfenylchlorides 7 and 8, (Scheme 2). The structure of these products was assigned on the basis of spectroscopic data and elemental analyses. The imidoyl chloride formation from the reaction of thionyl chloride on amides was confirmed from literature reports¹¹ and is analogous to the reaction on amides with phosphorus chlorides¹² or phosgene,¹³ corresponding to an imidoyl chloride formation *under conditions of the von Braun reaction*.

The foregoing results are consistent with a reactions' sequence involving conversion of 5→7→11 and 6→8→12, although, as was determined at periodically intervals by ¹H NMR spectroscopy, the fast conversion of 6d→12d for instance, was revealed without observation of the intermediate 8d. The gradual disappearance, of methylene protons (q, δ 2.25), methyl protons (t, δ 1.13) of the ethyl group and the N-benzylic protons signal (d, δ 4.35) of 6d, with the synchronous appearance of methyl protons signal (s, δ 2.32) and the new benzylic protons signal (s, δ 4.78) of 12d, was observed. Analogous was the conversion of 6h→12h, the gradual disappearance of two methylenes multiplet (m, δ 2.33-3.23) and the N-benzylic protons (d, δ 4.30) with the synchronous appearance of two new benzylic methylenes (q, δ 3.60 and 3.86, J = 15 Hz, AB system) corresponding to the PhCH₂- and a downfield shifted (s, δ 4.58) for the p-ClC₆H₄CH₂N= was observed. This monitoring showed that the rate of α -chloro chlorosulfenylation and imidoyl chloride formation appears to be the same. The same rate of conversion was also observed when we tested some of these reactions using dry carbon tetrachloride as reaction's solvent and one more thionyl chloride than theoretically needed, (1:4 instead of 1:3). Although the case of phenylacetic acid amides 5 mechanistically could be confirmed to the literature reports^{1,2,3} as benzylic oxidations, the case of propionic and β -phenylpropionic acid amides 6 do not fall into the case of methylenes' oxidation *alfa* to an enolizable carbonyl group, (e.g. ketonic or carboxylic acid chloride), and then the consequent electrophilic addition of thionyl chloride to the carbon-carbon double bond of the enol. This hypothesis is rather speculative for amides and do not coincide with one of the two above referred instances, (benzylic oxidation or electrophilic addition to a double bond). On the contrary, the imidoyl chloride formation could be explained through the corresponding enol-imine, [$\text{=C-C(=O)-NH-} \leftrightarrow \text{=C-C(-OH)=N-} \rightarrow \text{=C-C(Cl)=N-}$].



Scheme-2

These observations led to the conclusion that the amides under tested conditions are just another e of active methylene compounds oxidizable with thionyl chloride to the corresponding α -

chlorosulfenyl chlorides by attack on the methylene moiety *alpha* to carbonyl amide function, while the synchronously formation of the imidoyl chloride moiety appears to be favored when heterocyclization is diminished, (e.g. because of ring strain). We have found no prior reference in the literature to the formation of the bifunctional sulfenyl chlorides-imidoyl chlorides. Besides the efficiency of the method, plus the good yields, (75-87 %), and the relative stability¹⁴ of the products, this new functionalization may have high potential for synthetic problems. Except the usefulness of chlorosulfenyl moiety for heterocyclization (e.g. by electrophilic, addition or aromatic substitution or nucleophilic displacement), the imidoyl chloride moiety has also been used in cross-coupling¹⁵ reactions with organotin compounds and for coupling reactions¹⁶ with vinylmagnesium bromide to give unsaturated imines, ketones, enol-imines or enamines, depending on the reaction conditions. Though the generality of this reaction and the mechanism by which these products were being formed have not been thoroughly investigated, initial experiments with other β -substituted propionamides appear to work analogously. The expansion of the method to amides with longer carboxylic acids' chain as well as reactions of the produced chlorosulfenyl chlorides-imidoyl chlorides as electrophiles is currently being investigated.

Experimental

General. NMR spectra were recorded at ambient temperature using a Varian Gemini 2000 300 MHz spectrometer. The data are reported as follows: chemical shift are quoted in ppm on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants are given in (Hz). Micro analyses were performed by microanalytical laboratory of CNRS (France). Melting points are reported uncorrected. IR spectra were obtained at a Nicolet Magna 560 spectrometer (as nujol mulls). 70eV Electronic impact mass spectra were recorded on a Delsi-Nermag R-1010c spectrometer.

General procedure for the preparation of **11**: A solution of the amide **5d** (2g, 7.70 mmol) and 20 ml of freshly distilled thionyl chloride was stirred at room temperature, in a flask protected with a calcium chloride drying tube. After six days the excess of thionyl chloride was removed in vacuum, (the large amount is collected for reuse). The resulting solid was recrystallized from petroleum ether, (40-60 °C), to give an analytical sample of the product **11d**, 2.54 g, 87 % yield, mp 90-91 °C: Anal. Calcd for C₁₅H₁₁Cl₄NS: C, 47.52; H, 2.92; Cl, 37.40; N, 3.69; S, 8.45. Found: C, 47.51; H, 2.77; Cl, 37.40; N, 3.66; S, 8.51. IR (Nujol mull, cm⁻¹): 1686, 1602, 1592. ¹H NMR (300 MHz, CDCl₃): 4.80 (s, 2H, ArCH₂N=), 7.03-7.81 (m including a sharp s at 7.35, 9H, arom.). ¹³C NMR (75.5 MHz, CDCl₃): 56.06, 78.61, 127.20, 127.80, 128.82, 130.54, 137.01, 139.51, 164.70. HRMS (EI) calcd for C₁₅H₁₁Cl₄NS: 379.1315. Found: 379.1327.

General procedure for the preparation of **12**: A solution of the amide **6f** (4 g, 16.71 mmol) and 35 ml of freshly distilled thionyl chloride was refluxed, on a steam bath, for 2h, (no initial signals of the amide could be detected in the ¹H NMR spectrum of a sample taken at that time), the excess of thionyl chloride was then removed under vacuum, (as above). The solid residue was recrystallized from petroleum ether, (40-60 °C), to give an analytical sample of the product **12f**, 4.95 g, 82 % yield, mp 54-55 °C: Anal. Calcd for C₁₆H₁₄Cl₃NS: C, 53.57; H, 3.93; Cl, 29.65; N, 3.90; S, 8.94. Found: C, 53.64; H, 3.85; Cl, 29.71; N, 3.76; S, 9.20. IR (Nujol mull, cm⁻¹): 1686, 1615, 1592. ¹H NMR (300 MHz, CDCl₃): 3.72 (apparent t, J = 16 Hz, distorted AB system, 2H, PhCH₂C=), 4.62 (s, 2H, PhCH₂-N=), 6.70-7.43 (m, 10H, arom.). ¹³C NMR (75.5 MHz, CDCl₃): 38.80, 54.76, 76.03, 125.80, 126.03, 128.70, 138.93, 139.51, 165.67. HRMS (EI) calcd for C₁₆H₁₄Cl₃NS: 358.7131. Found: 358.7158

References and Notes

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