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AN UNUSUAL REACTION OF THIONYL CHLORIDE WITH AMIDES AND EASILY ENOLIZABLE KETONES

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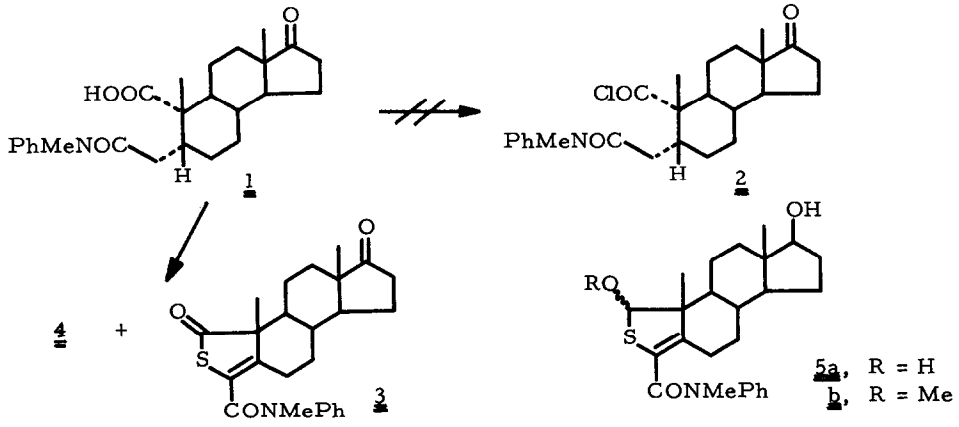
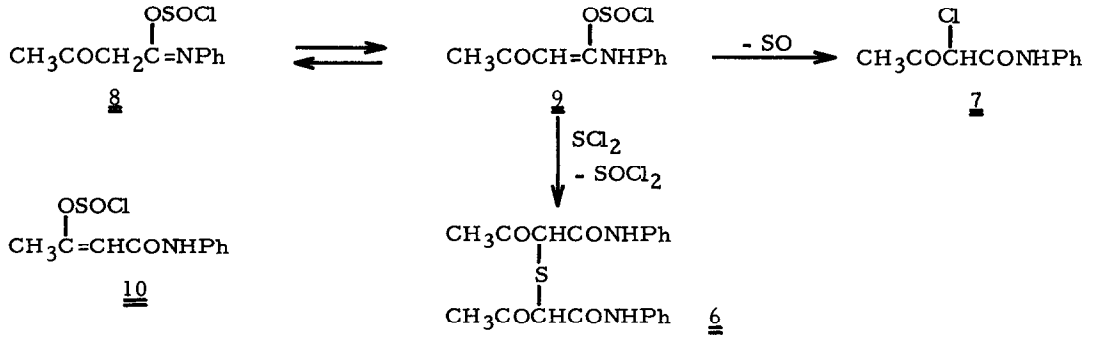
During our course of total synthesis of salamander alkaloids,[1] necessity compelled us to prepare a seco acyl chloride 2. However, all efforts to obtain the desired compound failed. When thionyl chloride was used in benzene containing pyridine, a sulfur containing material 3 (61%, mp 190-191°C; λ_{max}^{EtOH} nm (ε) 210 (14,500), 250 (7,300); NMR ($CDCl_3$) δ 0.86 (s, 18-CH_3), 0.96 (s, 19-CH_3), 3.45 (s, NCH_3); IR (KBr) 1742, 1696, 1650; MS 423 (M^+); Anal. Calcd. $C_{25}H_{29}NO_3S$: C, 70.90; H, 6.90; N, 3.31; O, 11.33; S, 7.56 Found: C, 71.14; H, 7.04; N, 3.11; O, 11.11; S, 7.32) and a structure-unknown chlorine containing compound 4 (13%, mp 175-177°C) were obtained. The former product was also prepared from the 5α-isomer in 60% yield. The structure of 3 was further confirmed by chemical conversion into the diol 5a (mp 242-244°C) and its monomethyl ether 5b (mp 187-189°C).



We could not find any convenient mechanism to explain the formation of 3. Other recent reports on the synthesis of sulfur containing heterocyclic compounds from active methylene compounds by the action of thionyl chloride also fail to explain the mechanism for this reaction.[2] Many of these heterocyclic syntheses can be reasonably explained by the chlorosulfenylation mechanism.[2a,c,d,3] Such chlorosulfenylation with thionyl chloride now seems to be of considerable generality.[4]

Lacking an explanation for the mechanism of the above mentioned reaction, we attempted to perform the same reaction on a series of simpler compounds. We wish to report a new type of reaction of amide or easily enolizable ketone with thionyl chloride to afford both the sulfide and chloride at the same time, owing to the production of sulfur dichloride in the reaction medium.

Acetoacetanilide[5] in absolute ether was treated with 1.5 molar equivalents of thionyl chloride at room temperature. The acetoacetanilide immediately dissolved with subsequent appearance of colorless crystals and change of solution color to orange. After two hours, the crystals again dissolved, and after three hours, a final crop of crystals appeared. These crystals consisted of two components which were separated by silica gel column chromatography wherein one product was assigned as di(acetylphenylaminocarbonylmethyl) sulfide 6 (58%, mp 143-145°C (lit.[6] 147°C); NMR ($CDCl_3$) 53% of the enol form, δ 2.27 (s, 3.2H, CH_3C=C), 2.44 (s, 2.8H, CH_3C=O), 4.05 (s, 0.9H, SCH), 6.9-7.4 (m, 10H, Ph), 8.6 (b, 2H, NH), 16.0 (b, 1.1H, OH); IR (KBr) 3325, 3230, 1716, 1648) and the other was α-chloroacetoacetanilide 7 (25%, mp 136-138°C; NMR ($CDCl_3$) δ 2.44 (s, 3H, CH_3), 4.92 (s, 1H, CHCl), 7.0-7.5 (m, 5H, Ph), 8.07 (b, 1H, NH); IR (KBr) 3225, 1740, 1654).



$$SO + SOCl_2 = SCl_2 + SO_2 \quad \cdots\cdots\cdots \text{(Eq. 1)}$$

The analogous sulfide formation from ethyl acetoacetate (vide infra) suggested tentatively the intermediacy of enolized chlorosulfite 10 for this reaction. However, the IR spectrum of the unstable crystals (mp 79-80°C; IR (nujol) 1720 (C=O))[7] which appeared at the early stage of the reaction showed absence of the amido group thus compelling us to consider the intermediate of this reaction must be the iminochlorosulfite 8.

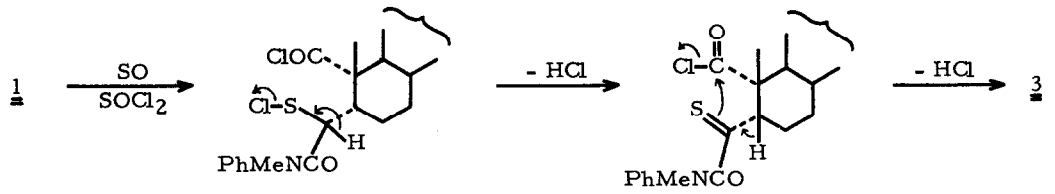
Our proposal for the mechanism is as follows. The amido group of acetoacetanilide reacts rapidly with thionyl chloride forming the iminochlorosulfite 8 which seems to be in equilibrium with the vinyl chlorosulfite 9 from which the α-chloride 7 is formed slowly by extrusion of sulfur monoxide. It is very probable that sulfur monoxide is in equilibrium with sulfur dichloride and sulfur dioxide in the presence of thionyl chloride (Eq. 1).[8] Sulfur dichloride thus formed reacts with the vinyl chlorosulfite 9 to give the sulfide 6[9]

competitively with the α-chlorination, releasing thionyl chloride or some other substance(s).

The reaction of the easily enolizable ketones with thionyl chloride proceeded essentially by the same sequence as above, except that the formation of vinyl chlorosulfite is comparatively slow. Thus ethyl acetoacetate gave the sulfide (mp 85-87°C, enol form by NMR; lit. 83-84°C,[9] 100-101°C[10]) and chloride (liq.) in the appropriate yields. As the molar ratios of thionyl chloride to ethyl acetoacetate were increased, the yields of the sulfide were also increased gradually. For the ratios of thionyl chloride employed, 1.4, 2.0, and 17.0, the yields of the sulfide were 19, 22, and 40%, respectively. This is explained in terms of shifting the equilibrium (Eq. 1) toward the formation of more sulfur dichloride.[11]

From this point of view, the formation of the thiol lactone 3 seems to be quite reasonable as described in Scheme I. Unfortunately, we could not assigned the structure of the other fragment 4 which had probably exposed to further chemical modifications in the medium.

Scheme I



It is worth mentioning that the known abnormal reaction of the vinylogous amide, 6-methylamino-1,3-dimethyluracil, with thionyl chloride to give 6-methylamino-1,3-dimethyl-5-chlorouracil and di(6-methylamino-1,3-dimethyluracil-5-yl) sulfide by Goldman[12] is now easily understandable in terms of sulfurization with sulfur dichloride produced in the reaction medium.[13] Goldman insisted that the yields of sulfide were dependent on the purity of thionyl chloride employed, the highest rates and yields of sulfide being realized with old samples of lower grade thionyl chloride, presumably owing to the presence of sulfur chloride(s). However, this does not explain why freshly prepared reagent gave almost the same results. It would seem that thionyl chloride distilled during usual pretreatment[14] is sufficiently pure and the explanation must be more involved.

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(5) The following compounds gave the analogous results: K. Oka and S. Hara, unpublished results. $PhCH_2CONHPh$, $CH_2(CONHPh)_2$

(6) K.G. Naik and V.B. Thosar, J. Indian Chem. Soc., 9, 471 (1932).

(7) Very sensitive to air and IR was taken after flash filtration with abs. n-hexane. Melting point was determined as usual, but was identical with the starting material.

(8) Similar equilibrium, $SO_2 + SOCl_2 = SCl_2 + SO_3$, has been used for the industrial preparation of thionyl chloride: U.S. Patent, 2,362,057.

(9) For preparation of the sulfide from sodium enolate of ethyl acetoacetate and SCl_2 see K. Buchka and C. Sprague, Chem. Ber., 22, 2541 (1889).

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(13) Using almost the same reaction condition, synthesis of 1,2,3-thiadiazolo [4,5-d] pyrimidines from 6-hydrazinouracil has been reported recently: K. Senga, M. Ichiba, and S. Nishigaki, Tetrahedron Letters, 1129 (1976). This reaction may be explained in terms of intramolecular cyclic sulfinylation of initially formed aminochlorosulfite of the primary amine in the usual manner.

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