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USE OF THIONYL CHLORIDE FOR IMINATION OF ACTIVE METHYLENE COMPOUNDS. CONVERSION OF α-CHLOROSULFENYL CHLORIDES TO IMINES VIA THIOCARBONYL S-IMIDES

Kitaro Oka* and Shoji Hara

Tokyo College of Pharmacy, Horinouchi 1432-1, Hachioji, Tokyo 192-03, Japan

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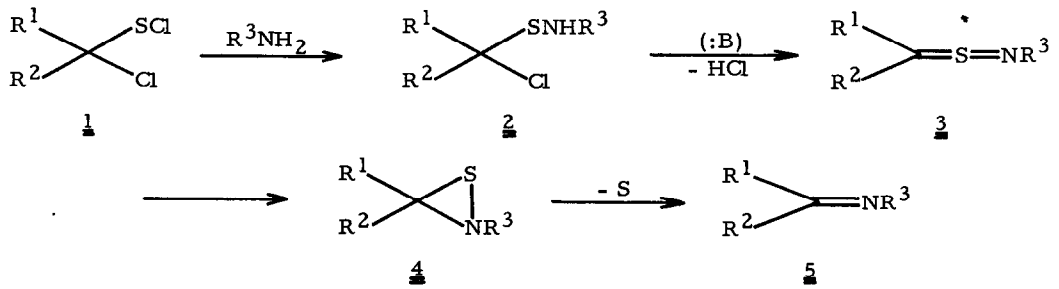
Recent reports[1a-f] on the synthesis and chemistry of thiocarbonyl S-imides[2] prompted us to report a novel synthetic method for the preparation of α-imino carbonyl compounds and their derivatives from α-chlorosulfenyl chlorides derived from active methylene compounds. Since mono-imination of α-diketones or direct amination of active methylene compounds is difficult, such imination of α-chlorosulfenyl chlorides affords a convenient method for the synthesis of these compounds.

We have recently reported[3] that active methylene compounds give α-chlorosulfenyl chlorides 1 when treated with thionyl chloride. α-Chlorosulfenamides 2 derived from such sulfenyl chlorides and primary amines can be readily converted to thiocarbonyl S-aryl or S-alkyl imides 3 which previously could not be synthesized. Our synthetic sequence for the preparation of thiocarbonyl S-imides and subsequent conversion to imino derivatives is illustrated in Scheme I.

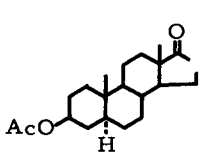
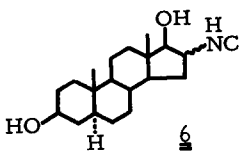
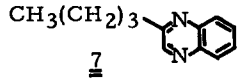
The requisite sulfenamides were prepared in high yields by treating α-chlorosulfenyl chlorides 1[3] with two molar equivalents of primary amines. Addition of one molar equivalent of amine produced an orange-red complex.[4] Subsequent treatment with a second molar equivalent of amine afforded the sulfenamides and amine hydrochloride quantitatively. The sulfenamides 2a, b, c, e, f derived from 1a, b, c, d were fairly stable and identified as assigned structures based on spectroscopic analyses: for example, 2a; yield, 94%;

Scheme I



1 2 3 4 5

Table I Synthesis of α-imino carbonyl compounds and their derivatives from α-chlorosulfenyl chlorides via thiocarbonyl S-imides.[a]

	Sulfenyl chloride 1		Amine	Condition		Product 5[b]			
						IR[c]		mp	Yield[d]
	R^1	R^2	R^3	- HCl	- S	C=O	C=N	(°C)	(%)
a	COOEt	COOEt	p-$MeOC_6H_4$	TEA, 60°C		1732	1630	—	83
b	PhCO	Me		TEA, r.t.	50°C	1665	—	—	66
c				TEA, r.t.	50°C	 6		185-186	46
d	PhCO	Ph	p-ClC_6H_4	none, r.t.		1667	1619	123-124	72
e			Ph	TEA or SiO_2, r.t.		1675	1622	103-104[e]	96
f			p-ClC_6H_4	TEA, r.t.		1660	1619	104-105	94
g			$PhCH_2$	none, r.t.		1673	—	—	68
h				none, r.t.		1669	1640	—	67
i	$CH_3(CH_2)_3$	CHO	o-$H_2NC_6H_4$	none, reflux		 7		—	47

(a) All reactions were carried out in benzene. (b) These imines were purified using HPLC techniques by employing an irregular shaped totally porous silica gel column (particle size: 50 μ, Wako Gel LC-50, Wako Pure Chem. Ind., Osaka). (c) KBr tab. for crystals and neat for oily products. (d) Based on active methylene compounds. (e) For preparation of this anil by oxidation of desoxybenzoin anil see Ref. 9: mp 105°C.

MS 347 (M^+, 11%), 311 (M^+ - HCl, 1%), 279 (M^+ - HClS, 5%);[5] NMR ($CDCl_3$) δ 1.10 (t, CH_3), 3.73 (s, CH_3O), 4.06 (q, CH_2), 5.33 (b, NH), 6.75 and 6.96 (ABq, J = 9 Hz, C_6H_4); IR (neat) 3345 (NH), 1730 (C=O).

However, other sulfenamides 2d, g, h decomposed immediately undergoing dehydrochlorination and desulfurization to yield their corresponding imino ketones 5d, g, h. The sulfenamides 2a, b, c, e, f were dehydrochlorinated with an equimolar amount of triethylamine. Dehydrochlorination of 2e proceeded more easily by treatment with silica gel. The unstable colored intermediates then decomposed to the imines 5a, b, c, e, f, respectively. These results are summarised in Table I.

The characteristic red color formation, compounds 2a-f, and blue color, compounds 2g, h, and production of free sulfur (86% for 2a) suggested that the imination process may proceeded through a thiocarbonyl S-imide 3 and thiazilidine intermediate 4 as reported by Oae et al.[1b] Thus we attempted the isolation of the thiocarbonyl S-imide 3b which seemed to be more stable than the others. Addition of one molar equivalent of triethyl-

amine to a solution of sulfenamide 2b in benzene at 10°C, followed by filtration of triethylamine hydrochloride and evaporation in vacuo, gave the deep-red thiocarbonyl S-imide 3b ($\lambda_{max}^{dioxane}$ 495 nm ($\varepsilon > 4200$), half-life at 25°C: ca 10 min). The wavelength of maximum absorption was nearly the same as analogous S-sulfonyl[1a,b] and S-benzoyl[1c] imides. All attempts to isolate the thiazilidine intermediate 4 have failed.

A typical procedure for the amination of an active methylene carbon is described below. The steroidal imino ketone 5c was reduced directly with sodium borohydride.

16-Chloro-16-chlorosulfenylepiandrosterone acetate 1c was prepared by refluxing epiandrosterone acetate (1 g) for 6 min in $SOCl_2$ (2 ml, 9 m. eq.)[6] containing pyridine (5 mg, 0.02 m. eq.). The excess reagent was evaporated in vacuo. To a solution of the residue in 10 ml of C_6H_6 cooled in an ice-water bath was added a solution of p-anisidine (741 mg, 2 m. eq.) in 10 ml of C_6H_6. The resulting mixture was kept at room temperature for 20 min until the orange color disappeared. Precipitated p-anisidine hydrochloride was filtered and the filtrate was treated with triethylamine (305 mg, 1 m. eq.) at 50°C for 2 hr. Precipitated triethylamine hydrochloride was filtered and the filtrate was concentrated to dryness. The residue was treated with 20 ml of EtOH containing 700 mg of $NaBH_4$ at reflux temperature for 1.5 hr. After the usual work-up, the crude amino alcohol 6 was purified by HPLC techniques mentioned in Table I to afford 630 mg of pure 6 (46% based on epiandrosterone acetate) which was recrystalized from EtOAc as prisms, mp 185-186°C; MS 413 (M^+, base peak); NMR ($CDCl_3$) δ 0.75 and 0.82 (two s, two CH_3), 3.44-3.82 (m, 3α,16ξ,17α-H_3), 3.71 (s, CH_3O), 6.64 and 6.76 (ABq, J = 9 Hz, C_6H_4).

To extend the scope of the reaction, we examined the chlorosulfenylation of an aliphatic aldehyde and the synthesis of an alkyl quinoxaline. When n-hexanal was treated with 15 molar equivalents of thionyl chloride in the presence of 0.10 molar equivalents of pyridine[7] at room temperature for 3 hours, 2-chloro-2-chlorosulfenyl-n-hexanal 1i was obtained in 65% yield: NMR ($SOCl_2$) δ 9.18 (s, CHO); IR (neat) 1730 (C=O). Compound 1i was treated with o-phenylenediamine in benzene at reflux temperature for 30 minutes to give 2-n-butylquinoxaline 7 in 47% yield based on n-hexanal: NMR (CCl_4) δ 0.97 (t, CH_3), 1.43 (m, CH_2), 1.85 (m, CH_2), 2.95 (t, $ArCH_2$), 7.5-8.1 (m, 4H, Ar), 8.63 (s, N=CH). Although the exact nature of the reaction is not known, it is worth mentioning that the extrusion of hydrogen sulfide instead of free sulfur was observed.[8]

REFERENCES AND NOTES

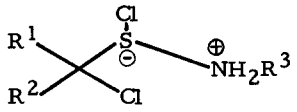
(1) (a) For the first synthesis of dithioester S-sulfonyl imides see S. Tamagaki and S. Oae, Tetrahedron Letters, 1159 (1972); (b) for thermal extrusion of sulfur see S. Tamagaki, K. Sakai, and S. Oae, Bull. Chem. Soc. Japan, 46, 2608 (1973); (c) for synthesis of thiocarbonyl S-benzoyl imides and their cyclization to 1,3,4-oxathiazoles see E.M. Burgess and H.R.

Penton, Jr., J. Am. Chem. Soc., 95, 279 (1973); J. Org. Chem., 39, 2885 (1974); (d) for synthesis of trithiocarbonate S-t-butyl imide see S. Holm, J.A. Boerma, N.H. Nilsson, and A. Senning, Chem. Ber., 109, 1069 (1976); (e) for separation of geometrical isomers and their photochemical extrusion of sulfur see A. Tangerman and B. Zwanenburg, Tetrahedron Letters, 259 (1977).

(2) This nomenclature was suggested by Burgess and Penton (see Ref. 1c).

(3) For preparation of 1a-d see K. Oka and S. Hara, Tetrahedron Letters, 695 (1977).

(4) Although these complexes seem to be sulfurane type ylides:



their existance was not determined. For analogous formation of the complex see E. Ciuffarin and G. Guaraldi, J. Am. Chem. Soc., 91, 1745 (1969). Quite recently a stable tricoordinate hypervalent sulfur compound has been reported: A.J. Arduengo and E.M. Burgess, ibid., 99, 2376 (1977).

(5) This fragmentation pattern is consistent with the degradation sequence shown in Scheme I.

(6) As the molar ratios of $SOCl_2$ to epiandrosterone acetate were increased, the yields of 1c were decreased gradually. For the ratio of 9 m. eq. of $SOCl_2$, the best yield of 1c was obtained ($>95\%$ based on NMR). The side product was 16-chloroepiandrosterone acetate. Large excess of $SOCl_2$ (70 m. eq.) and prolonged heating (2-3 hr) afforded this mono-chloride quantitatively. These unexpected results may be reported elsewhere in detail.

(7) Although 1,1-dichloro-n-hexane (NMR ($SOCl_2$) δ 5.80 (t, J = 6 Hz, $CHCl_2$)) was the predominent product when the reaction was carried out without pyridine, the addition of 0.10 m. eq. of pyridine completely suppressed the formation of this dichloride. For analogous dichlorination of carbonyl groups see (a) A. Schönberg and A.F.A. Ismail, J. Chem. Soc., 200 (1945); (b) A. Schönberg and R. von Ardenne, Chem. Ber., 101, 346 (1968).

(8) For analogous extrusion of H_2S about the phenylacetic acid derivative in the synthesis of 2-hydroxy-3-arylquinoxaline see M.S. Simon, J.B. Rogers, W. Saenger, and J.Z. Gougoutas, J. Am. Chem. Soc., 89, 5838 (1967). We examined the method for general synthesis of 2-hydroxy-3-alkylquinoxaline from fatty acids, for instance, 2-hydroxy-3-hexadecylquinoxaline from stearic acid in good yield: mp 108-110°C. For the synthesis of 2-mercapto analogues from methyl ketones see K. Oka and S. Hara, Heterocycles, in press.

(9) E. Knövenagel and O. Goos, Chem. Ber., 55, 1929 (1922).