The Preparation of 2-Chloroformyl-3-phenylthiazolo[3,2-a] pyridinium Chlorides from Cinnamic Acids, Pyridine and Thionyl Chloride

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2-Chloroformyl-3-phenylthiazolo[3,2-a]pyridinium chlorides are among the by-products obtained when 3-chlorobenzo[b]thiophene-2-carbonyl chlorides are prepared by the reaction of ciunamic acids with thionyl chloride and pyridine.

In a recent publication (1), we described the formation of 3-chlorobenzo [b] thiophene-2-carbonyl chlorides (1) by heating cinnamic acids (II) with thionyl chloride and pyridine. Among the unexpected by-products of these reactions was a series of precipitates which have now been identified as 2-chloroformyl-3-phenylthiazolo-[3,2-a] pyridinium chlorides (III).

When a mixture of cinnamic acid (II, R = II), thionyl chloride (5 equiv.), pyridine (0.1 equiv.) and toluene or chlorobenzene was heated for 24-72 hours at reflux temperature, a precipitate separated, while the desired 3-chlorobenzo[b]thiophene-2-carbonyl chloride (I, R = II) remained in solution. Microanalysis indicated an empirical formula of $C_{14}H_9Cl_2NOS$. This compound reacted rapidly when warmed with water or ethanol to give products of empirical formulas $C_{14}H_{10}ClNO_2S$ and $C_{16}H_{14}ClNO_2S$, respectively. Examination by ir, uv and nmr suggested that the compounds were 2-chloroformyl-3-phenylthiazolo[3,2-a]pyridinium chloride (III, R = II) and the corresponding acid (IV, R = II) and ethyl ester (Va).

The structure of these compounds has been confirmed by X-ray analysis (2) of the methyl ester (analogous to Va). Compound Va was also converted to the perchlorate salt (Vb) and this was shown to be identical by ir, uv and nmr (see Experimental) to the compound prepared by cyclization of ethyl α -(2-pyridylthio)benzoylacetate (VI) by the procedure of Bradsher and Lohr (3) for related thiazolo[3,2-a]pyridinium salts.

Similar reactions with p-chloro-, p-fluoro- and p-nitrocinnamic acids (II) resulted in the formation of the analogous p-substituted derivatives of structures III, IV and V (Table I). The yields of III were nearly quantitative based on the pyridine used, but were only about 10% based on the cinnamic acid. Attempts to increase the yield by raising the pyridine/cinnamic acid ratio gave a product of poorer quality and little increase in yield.

EXPERIMENTAL

The preparation of the compounds is described below using general procedures. Analyses, physical properties and important variations from these procedures are recorded in the Table. Melting points are uncorrected. Nmr data were determined with a Varian HA-100 spectrophotometer, using tetramethylsilane as internal standard and DMSO-d $_6$ as solvent. The following abbreviations are used in reporting nmr data: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. The ultraviolet spectra were measured with a Cary model 11 spectrometer, using methanol as solvent.

TABLE I
Thiazolo[3,2-a] pyridinium Chlorides

$$\begin{array}{c|c} & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\$$

R	R_1	M.p., °C (a)	Formula	Anal.	C, %	Н, %	Cl, %	F, %	N, %	S, %
Cl	Н	300	$C_{14}H_9Cl_2NOS(b)$	Caled. Found	54.2 54.3	2.9 3.0	$\frac{22.9}{22.6}$		4.5 4.4	$10.3 \\ 10.2$
ОН	Н	180	$\mathrm{C_{14}H_{10}ClNO_{2}S}$	Calcd. Found	57.6 57.6	3.5 3.5	$\frac{12.2}{12.2}$		4.8 4.8	$\begin{array}{c} 11.0 \\ 11.2 \end{array}$
OCH ₃	Н	300	$C_{15}H_{12}CINO_2S$	Caled. Found	59.0 59.0	3.9 4.0	11.6 11.9		4.6 4.5	10.5 10.5
OC_2H_5	Н	183	$C_{16}H_{14}CINO_2S$	Calcd. Found	60.1 59.7	4.4 4.4	11.1 11.1		$\frac{4.4}{4.3}$	10.0 10.0
Cl	F	300	$C_{14}H_8Cl_2FNOS$ (b)	Caled. Found	51.2 51.2	$\frac{2.5}{2.5}$	21.6 21.8	5.8 5.9	4.3 4.0	9.8 9.9
ОН	F	190	$C_{14}H_9CIFNO_2S$	Calcd. Found	54.3 54.2	2.9 2.9	$\frac{11.4}{11.7}$	$6.1 \\ 6.5$	4.5 4.4	$\frac{10.4}{10.1}$
OCH ₃	F	230	$C_{15}H_{11}CIFNO_2S$	Caled. Found	55.7 55.5	3.4 3.5	$11.0 \\ 11.2$	$\begin{array}{c} 5.9 \\ 6.2 \end{array}$	$\frac{4.3}{4.1}$	9.9 9.8
OC_2H_5	F	190	$C_{16}H_{13}ClFNO_2S$	Calcd. Found	56.9 57.1	3.9 3.8	10.5 10.8	5.6 5.7	4.1 4.0	9.5 9.6
ОС ₃ Н ₇	F	208	$C_{17}H_{15}CIFNO_2S$	Calcd. Found	58.0 57.6	4.3 4.6	10.1 9.9	5.4 5.5	4.0 4.0	9.1 8.8
OC ₄ H ₉	F	208	$C_{18}H_{17}ClFNO_2S$	Calcd. Found	59.1 58.8	4.7 4.7	9.7 9.9	5.2 5.6	3.8 4.1	8.8 8.8
Cl	Cl	310	$C_{14}H_8CI_3NOS$ (b)	Calcd. Found	48.8 48.4	$\frac{2.3}{2.7}$	30.9 30.1		4.1 3.9	9.3 9.5
OH	Cl	215	$\mathrm{C_{14}H_{9}Cl_{2}NO_{2}S}$	Calcd. Found	51.6 51.4	2.8 2.8	$21.7 \\ 21.5$		4.3 4.3	9.8 10.0
OC_2H_5	Cl	180	$C_{16}H_{14}Cl_{2}NO_{2.5}S$ (c)	Caled. Found	$52.9 \\ 52.6$	3.9 3.8	19.5 20.0		3.9 3.8	8.8 8.8
Cl	NO ₂	285	$C_{14}H_8Cl_2N_2O_3S$ (b)	Calcd. Found	47.3 46.4	$\frac{2.3}{2.6}$	$\frac{20.0}{19.7}$		7.9 7.8	9.0 8.8
ОН	NO ₂	200	$\mathrm{C_{14}H_{9}CIN_{2}O_{4}S}$	Calcd. Found	49.9 49.8	$\frac{2.7}{2.7}$	10.5 10.2		8.3 8.3	9.5 9.5

(a) Approximate decomposition points. In most samples, darkening and changes in the appearance of the crystals occurred at lower temperatures. (b) Crude product, analyzed as isolated without further purification. (c) Hemihydrate, Karl Fischer, 2.8%.

2-Chloroformyl-3-phenylthiazolo[3,2-a]pyridinium Chlorides.

A mixture of 0.1 mole of the cinnamic acid, 0.01 mole of pyridine, 0.5 mole of thionyl chloride and 100 ml. of toluene or chlorobenzene was heated at reflux temperature for 24-72 hours and filtered while hot to remove the insoluble 2-chloroformyl-3-phenylthiazolo[3,2-a]pyridinium chloride. The product was washed first with benzene and then with hexane, dried in a vacuum oven, and analyzed without further purification.

2-Carboxy-3-phenylthiazolo[3,2-a]pyridinium Chlorides.

Two grams of the 2-chloroformyl-3-phenylthiazolo [3,2-a]-pyridinium chloride was heated to solution in about 40 ml. of

water and allowed to stand overnight in the cold room. The precipitate was filtered off and recrystallized from water containing a little 6N hydrochloric acid.

2-Carbalkoxy-3-phenylthiazolo[3,2-a] pyridinium Chlorides.

A mixture of the 2-chloroformyl-3-phenylthiazolo[3,2-a]-pyridinium chloride and about 6 parts of the appropriate alcohol was heated to solution, allowed to stand at room temperature overnight, cooled and filtered. The product was generally analyzed without further purification.

 $\hbox{$2$-Carbethoxy-$3$-phenylthiazolo} \hbox{$[3,2$-$a]pyridinium} \ \ \hbox{Perchlorate}.$

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A solution of 400 mg. of 2-carbethoxy-3-phenylthiazolo [3,2-a]-pyridinium chloride, prepared by the above procedure, in 20 ml. of water was treated with 0.2 ml. of 70% perchloric acid. The white precipitate which separated was filtered off and recrystallized from ethanol. The yield of 2-carbethoxy-3-phenylthiazolo [3,2-a]-pyridinium perchlorate, m.p. 204-206°, was 290 mg.; uv (methanol) 205 m μ (log ϵ 4.48); 234 (4.33); 314 sh (4.07); 323 (4.13); nmr δ 1.06 (3H, t, J = 7 Hz), 4.25 (2H, q, J = 7), 7.68 (5H, s), multiplets (4H) at 7.93, 8.49, 8.67, 8.94.

Anal. Calcd. for $C_{16}H_{14}CINO_6S$: C, 50.1; H, 3.7; Cl, 9.2; N, 3.7; S, 8.4. Found: C, 49.8; H, 3.7; Cl, 9.1; N, 3.5; S, 8.3. B. From 2-Mercaptopyridine.

Sodium (1.2 g., 0.05 mole) was dissolved in 90 ml. of absolute ethanol and 5.5 g. (0.05 mole) of 2-mercaptopyridine was added. The mixture was stirred for 30 minutes and 13.6 g. (0.05 mole) of ethyl α-bromobenzoylacetate was added in portions. Stirring was continued for 18 hours at room temperature and the precipitated salt was filtered off. The reaction mixture was concentrated and the residue was dissolved in 150 ml. of benzene and washed twice with water. The benzene layer was concentrated to 11.7 g. of dark brown oil. Tlc indicated a mixture of two major and three minor products. Attempts to purify by chromatography were only partially successful as some decomposition occurred during the process.

A sample of the above crude ethyl $\alpha(2$ -pyridylthio)benzoylacetate was "purified" by thin layer chromatography on silica gel

plates using 9/1 heptane/THF. Band #3 was eluted with acetone and concentrated. A mixture of 600 mg. of this oil and 2 ml. of concentrated sulfuric acid was allowed to stand overnight at room temperature, poured into 50 ml. of cold ether and kept overnight in the cold room. The ether was decanted and the residue was dissolved in 5 ml. of water and treated with 4 ml. of 37% perchloric acid. An oil separated and gradually crystallized. The crystals were filtered, washed with water and dried in a vacuum oven. The yield was 389 mg., m.p. 160°. Recrystallization four times from ethanol resulted in pure 2-carbethoxy-3-phenylthiazolo-[3,2-a]pyridinium perchlorate, m.p. 204-206°. This compound was identical to the previous sample by ir, uv and nmr. Acknowledgments.

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REFERENCES

- (1) W. B. Wright, Jr. and H. J. Brabander, J. Heterocyclic Chem., 8, 711 (1971).
 - (2) D. B. Cosulich and F. M. Lovell, to be reported.
- (3) C. K. Bradsher and D. F. Lohr, Jr., J. Heterocyclic Chem., 3, 27 (1966).