Acetylpyridinium as an Amino Protector Group

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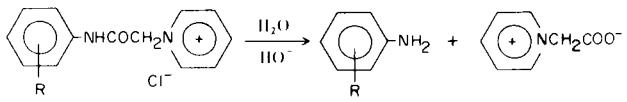
We reported in a previous paper (1) that the amide function of some acetylpyridinium anilides could be easily hydrolyzed by treatment with dilute alkali to give the corresponding amines:



This paper reports further study of the acetylpyridinium group as a suitable amino protector group in certain cases. The well known trifluoracetyl group as an amino protector group (2), presents some inconvenience during the deblocking process which limits its use. In fact, the required concentration of alkali during the deblocking process can produce the hydrolysis of adjacent amido groups and the low solubility of the trifluoroacetamide obliges the operator to reduce the initial concentration of the amide, making the unwanted hydrolysis side reaction more difficult to avoid.

To find another structure which would produce an effect similar to that of the trifluoromethyl group, it was thought that a quaternary nitrogen derivative might permit easy alkaline hydrolysis and could confer at the same time a high water solubility to the amide as occurs with the Girard reagents (3). The pyridinium derivative was more suitable because it could be produced (sometimes quantitatively) simply by heating the chloroacetylamide derivative with pyridine as recommended by Svetkim *et al.*, (4). This method was effective for the preparation of thirteen 1-carboxanilidomethylpyridinium chlorides and three 1-carboxamidomethylpyridinium chlorides, listed in Table I. They were isolated as water-soluble crystalline solids, the structures of which were confirmed by analysis and ir spectra.

Attempts to introduce the 1-carbonylmethylpyridinium group by other methods failed. For example, 1-chlorocarbonylmethylpyridinium chloride could not be obtained since the action of thionyl or oxalyl chloride caused the decarboxylation of the 1-carboxymethylpyridinium chloride. The ester 1-carbomethoxymethylpyridinium chloride could be prepared in alcoholic solution (5) but treatment of the solution with several amines failed to yield amides and instead afforded resins.

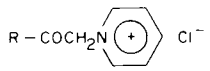
The stability tests for the 1-carboxanilidomethylpyridinium chloride and 1-carboxamidomethylpyridinium chloride reported here, were performed at 37° in concentrated and 10% hydrochloric acid. In these media twelve hours later no free amine was detected. Although the acetylpyridinium anilides and amides were satisfactorily hydrolyzed by 0.1 *N* sodium hydroxide at room temperature, all of the determinations were performed at 37° using 0.05 *N* sodium hydroxide in order to measure the relative rate of hydrolysis. This was expressed by the time in minutes required for the hydrolysis of 50% of the product. Two equivalents of alkali per mole of amide was used in each case. We also measured the stability of the 1-carboxamidomethylpyridinium hydroxides which were obviously formed in solution by reaction between the alkali and the acetylpyridinium amide chlorides. For this purpose we prepared 1-(*m*-trifluoromethylcarboxanilido)-methylpyridinium hydroxide by treating compound IX (Table I) with Amberlite IR 400 ion exchange resin in non-aqueous medium; a dense oil was obtained. The analysis and ir spectra of the oil were in agreement with the expected structure. The oil had a low stability at room temperature and afforded a resin at temperatures over 50°. The oil was very soluble in water giving strong alkaline reaction. The time of hydrolysis was similar to that of the corresponding chloride.

Relationship Between Structure and Relative Rate of Hydrolysis.

The 1-carboxamidomethylpyridinium salts (compounds XV and XVI) hydrolyzed more slowly than the 1-carboxanilidopyridinium salts. This was especially noticeable with those 1-carboxanilidopyridinium salts which contained electron attracting substituents (compounds V, VI, VII, VIII and IX). The pK_b of the starting amines proved to have limited influence on the rate, but the solubility of the liberated amines seemed to be important. All of the derivatives of the secondary amines showed a higher rate of hydrolysis (compounds XII, XIII, and XIV).

TABLE I

Amides



Compound	R-	Recrystn. Solvent	M.p., °C	Yield %	Ir data C=O band cm^{-1}	Formula	Analysis Calcd. % (Found %) C	H	N	Hydrolysis 50% (minutes)
I	C_6H_5NH-	a + b	(a)	92	1670	--		--		45
II	4-$CH_3C_6H_4NH$-	a + c	250-251	87	1670	$C_{14}H_{15}ClN_2O$	64.0 (64.2)	5.71 (5.95)	10.6 (10.4)	120
III	4-$CH_3OC_6H_4NH$-	a + c	186-187	82	1670	$C_{14}H_{15}ClN_2O_2$	60.3 (60.5)	5.38 (5.45)	10.1 (10.2)	27
IV	4-ClC_6H_4NH-	a	253-254	94	1670	$C_{13}H_{12}Cl_2N_2O$	55.1 (55.3)	4.24 (4.29)	9.88 (9.81)	76
V	4-$CO_2HC_6H_4NH$-	d	278-279	72	1670	$C_{14}H_{13}ClN_2O_3$	57.4 (57.3)	4.44 (4.51)	9.57 (9.51)	15
VI	4-$NO_2C_6H_4NH$-	a + b	280-281	93	1700	$C_{13}H_{12}ClN_3O_3$	53.1 (53.3)	4.09 (4.18)	14.3 (14.5)	22
VII	3-$NO_2C_6H_4NH$-	a	(a)	84	1700	--		--		33
VIII	4-$C_6H_5COC_6H_4NH$-	d + b	258-259	89	1700	$C_{20}H_{17}ClN_2O_2$	68.0 (68.2)	4.82 (4.93)	7.94 (7.87)	9
IX	3-$CF_3C_6H_4NH$-	a + c	215-216	91	1670	$C_{14}H_{12}ClF_3N_2O$	53.0 (52.8)	3.79 (3.94)	8.84 (8.89)	22
X	4-OHC_6H_4NH-	d + b	264-265	68	1670	$C_{13}H_{13}ClN_2O_2$	58.9 (58.6)	4.91 (5.09)	10.5 (10.4)	165
XI	β-$C_{10}H_7NH$-	d + b	(a)	88	1670	--		--		30
XII	$C_6H_5NCH_3$ |	d + e	138-139	52	1670	$C_{14}H_{15}ClN_2O$	64.0 (64.3)	5.71 (5.93)	10.6 (10.4)	15
XIII	$(C_6H_5)_2N$-	a	(a)	93	1670	--		--		7
XIV		b + f	128-129	89	1680	$C_{12}H_{17}ClN_2O$	59.8 (59.7)	7.12 (7.13)	11.6 (11.5)	13
XV	$C_6H_{11}NH$-	a + c	204-205	70	1680	$C_{13}H_{18}ClN_2O$	61.5 (61.7)	7.10 (7.20)	11.0 (11.2)	700
XVI	CO_2HCH_2NH-	f	208-209	84	1680	$C_9H_{11}ClN_2O_3$	46.8 (46.6)	4.77 (4.85)	12.1 (12.0)	450

(a) Compounds described by Svetkim (4), m.p. were coincident. Solvents: a, 2-propanol; b, benzene; c, ligroin; d, dimethylformamide; e, dioxane; f, ethanol.

It is suggested that the 1-carbonylmethylpyridinium group could be used to convert a water-insoluble amine to a soluble derivative easily hydrolyzed by dilute alkali.

EXPERIMENTAL

Melting points were taken in capillary tubes in a Buchi apparatus and are uncorrected. The infrared spectra were recorded on a Beckman Model IR 20 Spectrophotometer. Colorimetric titration was performed on a Bausch & Lomb Spectronic apparatus. Quantitative C, H, N analyses were performed in Facultad de Farmacia y Bioquimica and Facultad de Ciencias Exactas Laboratories, Buenos Aires.

1-Carboxamido and 1-Carboxanilidopyridinium Chlorides.

General Procedure.

A mixture of 5.0 g. of the corresponding chloroacetamide (or anilide) and 25 ml. of dry pyridine was heated for one hour on a steam bath. After cooling, the 1-carboxamido or 1-carboxanilidomethylpyridinium chloride precipitated either as a crystalline solid or as a dense oil. When pyridine-soluble products were obtained (compounds XII and XIV) the solvent was evaporated *in vacuo*. In each case the crude product was crystallized from a suitable solvent (Table I).

1-(*m*-Trifluoromethylcarboxanilido)methylpyridinium Hydroxide.

Fifty milliliters of Amberlite ion exchange resin IR 400 in a 30 cm length column was treated with 100 ml. of 3% sodium hydroxide, washed with water to *p*H 7.5-8 and dried by passing anhydrous methanol through it. A solution of 3 g. of 1-(*m*-trifluoromethylcarboxanilido)methylpyridinium chloride (IX) in 80 ml. of anhydrous methanol was passed through the column at a flow rate of 26 drops per minute; then a 25 ml. portion of methanol was added and the total effluent was collected and evaporated *in vacuo* at 35°; the desired product was a yellowish dense oil.

Anal. Calcd. for $C_{14}H_{13}F_3N_2O_2$: N, 9.39. Found: C, 9.32.

Hydrolysis of the 1-Carboxanilidomethylpyridinium Chlorides.

Each compound (0.175 mmole) was dissolved in 80 ml. of 0.05 *N* sodium hydroxide at 37°. An aliquot of 10.0 ml. was readily titrated with 0.05 *N* hydrochloric acid in presence of phenolphthalein. The same titrations were repeated at intervals of 15, 30, 69, 90 minutes and 24 hours. The time required for the hydrolysis of 50% of the product was calculated graphically.

Hydrolysis of Compounds XIV and XV.

Samples were dissolved in 0.05 *N* sodium hydroxide following the same procedure as above. An aliquot of 2.0 ml. of each compound was put into a 50 ml. volumetric flask; 0.2 ml. of 2.5% sodium borate.10 H_2O was added and the volume was completed with ethanol. An aliquot of 1.0 ml. of this solution was taken and 0.2 ml. of 5% 2,4-dinitrofluorobenzene in alcohol and 4.0 ml. of ethanol were added. This solution was heated at 90° for 5 minutes and then a colorimetric titration was performed at 385 mμ.

Samples of compound XV were taken at the same time intervals as for the carboxanilidomethylpyridinium compounds and compound XIV at intervals of 0, 30, 60, 400 minutes and 19 and 25 hours. The time required for 50% hydrolysis was determined graphically.

Hydrolysis of Compound XVI.

A sample was dissolved in 0.05 *N* sodium hydroxide as above. An aliquot of 2.0 ml. was neutralized with 0.05 *N* hydrochloric acid in presence of phenolphthalein. An aliquot of 1.0 ml. of the last solution was taken and 2 ml. of 2% ninhydrin in alcohol and 4.0 ml. of ethanol were added. This solution was then heated at 100° for 20 minutes. The time required for 50% hydrolysis was determined as above.

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REFERENCES

(1) C. H. Gaozza and S. Lamdan, *Tetrahedron Letters*, 4945 (1969).

(2) F. Weygand and E. Csendes, *Angew. Chem.*, 64, 136 (1952).

(3a) A. Girard and G. Sandulesco, British Patent application 6640 (1934). (b) A. Girard and G. Sandulesco, French Patent, 767,464 (1934).

(4) Yu. V. Svetkim, A. N. Minlibaeva and L. I. Vikhryakova, *Zh. Obshch. Khim.*, 32, 3227 (1962); *Chem. Abstr.*, 58, 10166 (1962).

(5) A. Girard and G. Sandulesco, *Helv. Chim. Acta*, 19, 1095 (1936).