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The Reactions of Several Anilides with Phosphoryl Chloride

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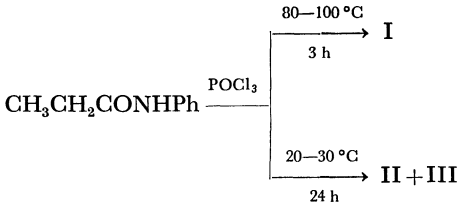
Synopsis. Chloroacetanilide and *p*-methylchloroacetanilide reacted with phosphoryl chloride to give 2-chloromethyl-3-chloro-4-anilinoquinoline and 2-chloromethyl-3-chloro-4-(*p*-toluidino)-6-methylquinoline respectively. In the case of propionanilide, 2-ethyl-3-methyl-4-anilinoquinoline was obtained when the reaction was carried out at 20—30 °C. On the other hand, when the reaction temperature was raised to 80—100 °C, *N*-(1-chloro-1-propenyl)-*N*,*N*′-diphenylacetamidine was obtained.

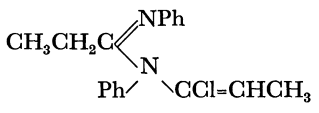
It is well known that a Vilsmeier reagent can be prepared from an *N*,*N*-disubstituted amide, such as *N*,*N*-dimethylformamide or *N*,*N*-dimethylbenzamide, with phosphoryl chloride.[1] *N*,*N*-Unsubstituted amides, such as acetamide and benzamide, are also known to be converted into the corresponding nitrile in good yields by treatment with phosphoryl chloride.[2] In this paper, we wish to report the reaction of anilides with phosphoryl chloride.

Results

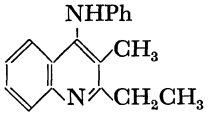
Propionanilide was allowed to react with phosphoryl chloride at 80—100 °C for 3 h, thus giving *N*-(1-chloro-1-propenyl)-*N*,*N*′-diphenylpropionamidine(I). When the reaction was carried out in the temperature range between 20 and 30 °C for 24 h, 2-ethyl-3-methyl-4-anilinoquinoline(II) and *N*,*N*′-diphenylpropionamidine (III) were obtained.



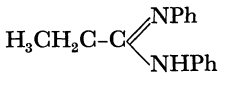
(1)



(I)

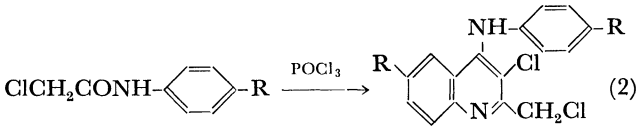


(II)



(III)

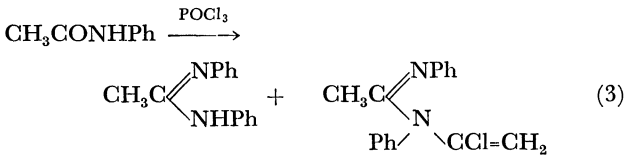
When chloroacetanilide(IVa) and *p*-methylchloroacetanilide(IVb) were used in place of propionanilide, 2-chloromethyl-3-chloro-4-anilinoquinoline(Va) and 2-chloromethyl-3-chloro-4-(*p*-toluidino)-6-methylquinoline(Vb) were isolated in 50—60 and 26% yields respectively. Amidine derivatives were not detected, regardless of the reaction temperature.



(2)

(IVa, R=H; IVb, R=Me) (Va, R=H; Vb, R=Me)

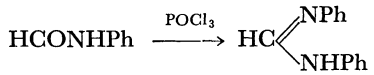
On the other hand, when the reaction of acetanilide with phosphoryl chloride was run at 80 °C for 3 h, *N*,*N*-diphenylacetamidine(VI) and *N*-(1-chlorovinyl)-*N*,*N*′-diphenylacetamidine(VII) were yielded in an equimolar ratio. When the reaction conditions were controlled at 20—30 °C for 24 h, the distribution of products VI and VII was changed to the molar ratio of 74 : 26.



(3)

(VI) (VII)

In the case of formanilide with phosphoryl chloride, *N*,*N*′-diphenylformamidine(VIII) was obtained in a 10% yield.



(VIII)

The results of these experiments are summarized in Table 1.

Experimental

All the melting and boiling points are uncorrected. The NMR spectra were measured at 100 MHz on a JNM-TS-100 spectrometer, with TMS as the internal reference in deuteriochloroform. The mass spectra were recorded on a Hitachi RMU-6 or RMU-7 spectrometer.

Materials. Commercial first-grade acetanilide and formanilide were used after recrystallization. Chloroacetanilide (mp 138 °C), *p*-methylchloroacetanilide (mp 163 °C), and propionanilide (mp 104 °C) were prepared in the usual way.

Reaction of Anilides with Phosphoryl Chloride. General Procedure: In a 150-ml flask fitted with a reflux condenser we placed 50 mmol of anilide and 55 mmol of phosphoryl chloride. The mixture was then magnetically stirred, and the temperature was maintained at 20—30 or 80—100 °C for an appropriate period. After cooling, the mixture was poured into 150 ml of ice water, the solution was then allowed to stand for an additional 24 h. The HCl salt of the quinoline derivative(II, V, and VIII) was precipitated if quinoline was present, and easily separated by filtration. The filtrate was extracted twice with ether to remove the unreacted anilide. The aqueous layer was neutrallized with a 1 M NaOH aq solution to pH 7. The crude amidine derivative (I or VII) was extracted with ether. The aqueous layer was treated

Table 1. The reaction of several anilides with phosphoryl chloride

Anilide	Temp (°C)	Time (h)	Product, isolated yield (%)	
			Quinoline derivative	Amidine derivative(s)
$HCONHC_6H_5$	20—30	1	0	10
$CH_3CONHC_6H_5$	20—30	24	0	78
	80—100	3	0	50
$CH_3CH_2CONHC_6H_5$	20—30	24	23	trace
	80—100	3	0	8
$ClCH_2CONHC_6H_5$	20—30	24	59	0
	80—100	3	50	0
$ClCH_2CONHC_6H_4 \cdot CH_3$-*p*	80	2	26	0

with a large amount of a 1 M NaOH solution. The amidines (III, VI, and VIII) were precipitated.

Physical Properties and Analytical Data of the Products. *Product I*: Bp 100 °C/10^{-4} Torr. NMR ($CDCl_3$): δ 1.00 (t, 3H, $-CH_2\underline{CH_3}$) 1.80 (d, 3H, $=CH\underline{CH_3}$) 2.45 (q, 2H, $-\underline{CH_2}CH_3$) 5.82 (q, 1H, $=\underline{CH}CH_3$) 6.7—7.6 (m, 10H, aromatic protons). MS: *m/e* (rel intensity) 298 (M^+ Cl^{35}, 2) 283 (11) 167 (15) 132 (100) 103 (18) 93 (69) 77(92). Found: Cl, 11.54%. Calcd for $C_{18}H_{19}N_2Cl$: Cl, 11.74%.

Product II: Mp 183 °C. NMR: δ 1.38 (t, 3H, $-CH_2\underline{CH_3}$) 2.30 (s, 3H, $-CH_3$) 3.05 (q, 2H, $-\underline{CH_2}CH_3$) 5.85 (br, 1H, NH) 6.5—8.1 (m, 9H, aromatic protons). MS: *m/e* 262 (M^+, 100) 245 (18) 234 (13). Found: Cl, 11.65%. Calcd for $C_{18}H_{18}N_2 \cdot HCl$: Cl, 11.89%. The product(II) had NMR and mass spectra identical with those of an authentic sample.[3]

Product III: Mp 100—102 °C. NMR: δ 1.10 (t, 3H, $-CH_2\underline{CH_3}$) 2.26 (q, 2H, $-\underline{CH_2}CH_3$) 5.8 (br, 1H, NH) 6.9—7.3 (m, 10 H, aromatic protons). MS: *m/e* 224 (M^+, 17) 132 (100) 104 (9) 77 (43). The product(III) had NMR and mass spectra identical with those of an authentic sample, which had been prepared from propionanilide and aniline by the method of Partridge and Smith.[4]

Product Va: Mp 133—133.5 °C. NMR: δ 4.96 (s, 2H, $-CH_2Cl$) 6.5—8.1 (m, 10 H, aromatic protons and NH). MS: *m/e* 302 (M^+ Cl^{35} Cl^{35}, 100) 267 (29) 231 (97) 115 (16) 102 (13) 77 (26). Found: C, 63.02; H, 3.87; N, 9.16%. Calcd for $C_{16}H_{12}N_2Cl_2$: C, 63.37; H, 3.96; N, 9.24%.

Product Vb: Mp 130—132 °C. NMR: δ 2.28 (s, 6H, two methyl groups) 4.88 (s, 2H, $-CH_2Cl$) 6.5—8.0 (m, 8H, aromatic protons and NH). MS: *m/e* 332 (Cl^{36} Cl^{36}, 75) 330 (M^+ Cl^{35} Cl^{35}, 100) 296 (30) 259 (75).

Product VI: Mp 131—132 °C. NMR: δ 2.00 (s, 3H, $-CH_3$) 6.15 (s, 1H, NH) 7.0—7.5 (m, 10 H, aromatic protons). MS: *m/e* 210 (M^+, 21) 118 (100) 93 (9) 77 (32). Found: C, 79.87; H, 6.66; N, 13.16%. Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32%.

Product VII: Mp 117.5—118.5 °C. NMR: δ 1.90 (s, 3H, $-CH_3$) 5.37 (d, $1H_a$, $=CH_aH_b$ J_{ab} 4Hz) 5.45 (d, $1H_b$) 6.7—7.4 (m, 10 H, aromatic protons). MS: *m/e* 270 (M^+ Cl^{35}, 16) 118 (100) 77 (76). Found: C, 70.93; H, 5.35; N, 10.21; Cl 13.60%. Calcd for $C_{16}H_{15}N_2Cl$: C, 71.11; H, 5.55; N, 10.37; Cl, 13.15%.

Product VIII: Mp 136—136.6 °C. NMR: δ 7.0—7.5 (m, 10 H, aromatic protons) 8.22 (br, 1H, NH) 8.55 (s, 1H, CH). MS: *m/e* 196 (M^+, 26) 104 (11) 93 (100) 77(26). Found: C, 79.40; H, 6.02; N, 14.22%. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28%.

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