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The Reaction of Oxalyl Chloride with Amides. III.[1] The Acylation of Amides

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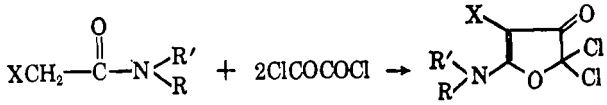
The reaction of N,N-disubstituted acetamides with oxalyl chloride to form furanone amines has been extended to include a variety of α-substituted acetamides. It has been found that α-chloroenamines and N,N-disubstituted thionamides also produce furanone amines on reaction with oxalyl chloride and that α-iodoamides yield 4-chlorofuranone amines. The reaction is discussed in the light of these observations and the mechanism which is proposed led to a new reaction for the formation of acetoacetic amides from treatment of amides with acid chlorides.

Our interest in the synthesis of α-chloroenamines by the treatment of N,N-disubstituted amides I with a variety of chlorinating agents led to an investigation of the reaction of N,N-disubstituted α-chloro- and α-phenylacetamides with oxalyl chloride. This reaction produced 5-(disubstituted amino)-4-chloro- or -phenyl-3(2H)-furanones (II)[2] rather than the chloroenamines and has now been extended to N,N-disubstituted acetamides possessing a variety of α substituents (Table I).



a, X = Cl; R′ = C_6H_5; R = CH_3
b, X = Cl; R′ = R = C_6H_5
c, X = C_6H_5; R = R′ = C_2H_5

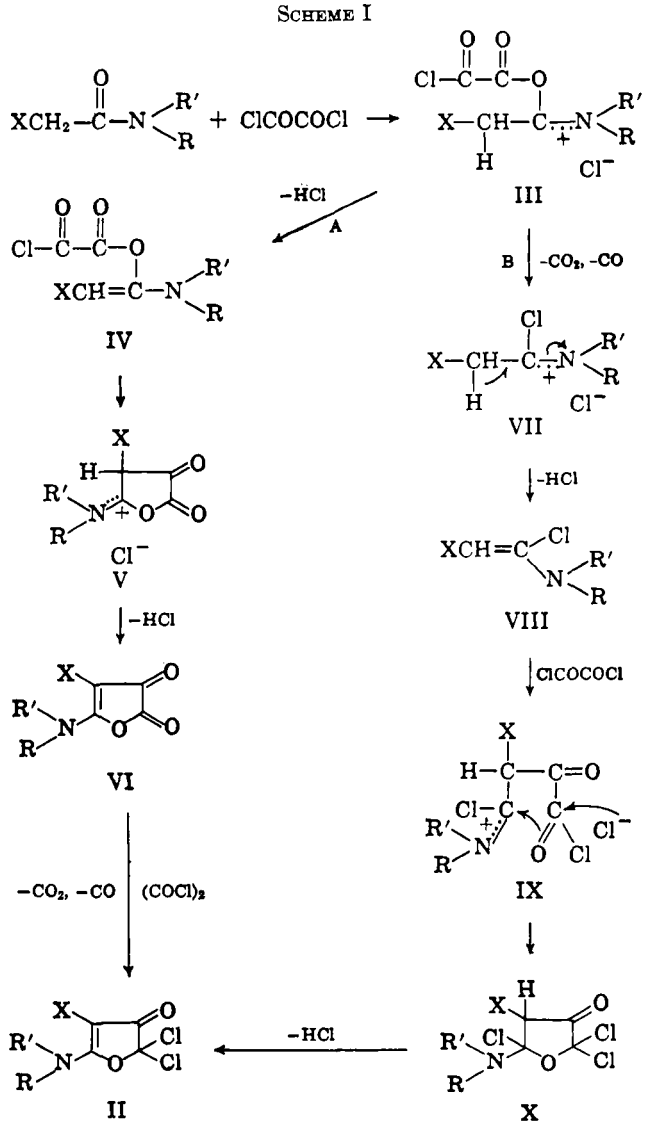
The conversion of an amide to a furanone amine may be visualized to occur principally by two pathways. (Scheme I).

O-Acylation of the amide to produce III is common to both. Pathway A (III → IV → II) would involve the dehydrochlorination of III to the aminovinyl ester IV which would lead to the furandione VI by intramolecular acylation. The chlorination of IV by oxalyl chloride would produce II.

Pathway B (III → VII → II) would proceed *via* the chloroenamine VIII which was initially sought. This enamine would, however, undergo further reaction with oxalyl chloride (acylation) to form IX. Attack of chloride ion on IX, followed by ring closure and loss of hydrogen chloride, would lead to II. In this sequence oxalyl chloride would not act as a chlorinating agent *per se*.

Differentiation between the two mechanisms might be achieved by the preparation of VI and its subsequent reaction with oxalyl chloride. Attempts to prepare the cyclic ketolactone VI by base-catalyzed cyclization of methyl N,N-diethyl-2-phenyloxalacetamate (XI) were not successful. Treatment of XI with refluxing pyridine or potassium *t*-butoxide in refluxing benzene led only to tar formation.

SCHEME I



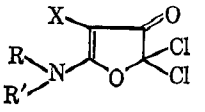
In view of these results, it was decided to establish the intermediacy of an enamine in pathway B by treating a chloroenamine, rather than an amide, with oxalyl chloride. Reaction of N,N-diphenyl-1,2-dichlorovinylamine[3] (VIII, X = Cl, R = R′ = C_6H_5)

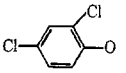
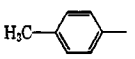
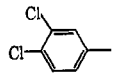
(1) For paper II in this series, see A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28**, 1805 (1963).

(2) A. J. Speziale and L. R. Smith, *ibid.*, **27**, 4361 (1962).

(3) A. J. Speziale and L. R. Smith, *J. Am. Chem. Soc.*, **84**, 1868 (1962).

TABLE I

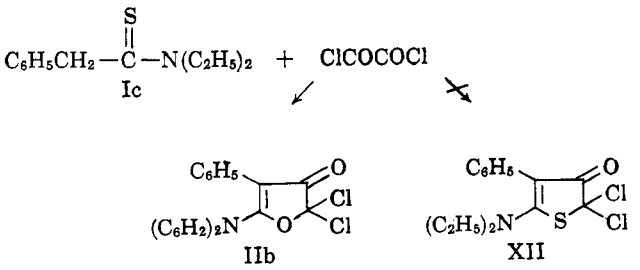


R	R′	X	M.p., °C.	Yield, %	λ_{max},[a] mμ (log ε)	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
CH_3	C_6H_5	C_6H_5O	109–111	63	317 (4.28) 218 (4.13)	58.31	3.74	4.00	20.25	58.43	4.05	4.20	20.55
CH_3	C_6H_5		152–154	70	313 (4.26) 230 (4.08)	48.72	2.65	3.34	33.83	48.95	3.13	3.58	32.98
CH_3	C_6H_5	CH_3O	105–107	76	325 (4.25) 230[b] (3.71)	50.02	3.85	4.86	24.62	50.30	3.83	4.81	24.26
C_2H_5	C_2H_5	C_6H_5O	95.5–96.5	82	311 (4.25) 214[b] (4.13)	53.16	4.78	4.43	22.43	53.27	4.87	4.39	22.22
C_2H_5	C_2H_5	CH_3	73–74.5	34	310 (4.31) 205[b] (3.89)	45.40	5.50	5.88	29.79	45.79	5.71	5.71	29.45
CH_3	C_6H_5	CN	191–193	32	288 (4.31) 223[b] (3.97)	50.90	2.85	9.90	25.05	51.06	4.11	9.63	25.34
CH_3	C_6H_5		161–162.5	56	318 (4.18) 247 (4.07)	62.09	4.34	4.02	20.36	61.61	4.28	3.98	20.54
C_2H_5	C_2H_5	C_6H_5S	90–92	34	291 (4.16) 248 (4.10) 240 (4.09)	50.61	4.55	4.22	21.34[c]	50.47	4.60	4.09	21.24
C_2H_5	C_2H_5		143–146	81	304 (4.25)	45.56	3.55	3.80	38.43	45.14	3.65	3.52	38.78

[a] In absolute ethanol on Beckman DK-2A. [b] Inflection. [c] *Anal.* Calcd.: S, 9.65. Found: S, 9.71.

with oxalyl chloride gave an 84% yield of 5-diphenylamino-2,2,4-trichloro-3(2H)-furanone (IIb).

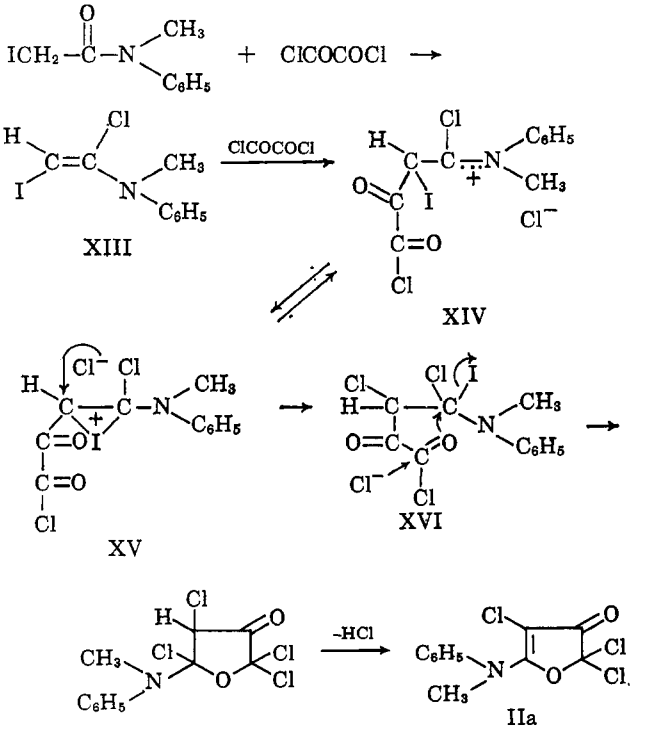
Further evidence for pathway B was found in the reaction of N,N-diethyl-2-phenylthionacetamide with oxalyl chloride. This reaction led to desulfurization of the thionamide and the isolation of 5-diethylamino-2,2-dichloro-4-phenyl-3(2H)-furanone (IIb). If pathway A were operative, a thiophenone derivative XII should have been isolated. Thus, although pathway



A has not been excluded, our experimental data strongly favor pathway B.

When N-methyl-α-iodoacetanilide was treated with oxalyl chloride, 5-methylanilino-2,2,4-trichloro-3(2H)-furanone (IIa) was isolated rather than the 4-iodo derivative. The exchange of iodine for chlorine could be explained on the basis of the sequence in Scheme II. The iodoenamine XIII would be formed and acylated (giving XIV) as postulated. However, in this case, an iodonium ion XV may be produced in which the three-membered ring may be opened by chloride ion attacking at C-1 or C-2. If attack occurs at C-1, XIV is regenerated, but if attack occurs at C-2, the iodine atom migrates to C-1. When this occurs, ring closure (of XVI) would lead to the displacement of iodide ion giving XVII and subsequently IIa. The displacement of iodide ion for chloride ion in either

SCHEME II

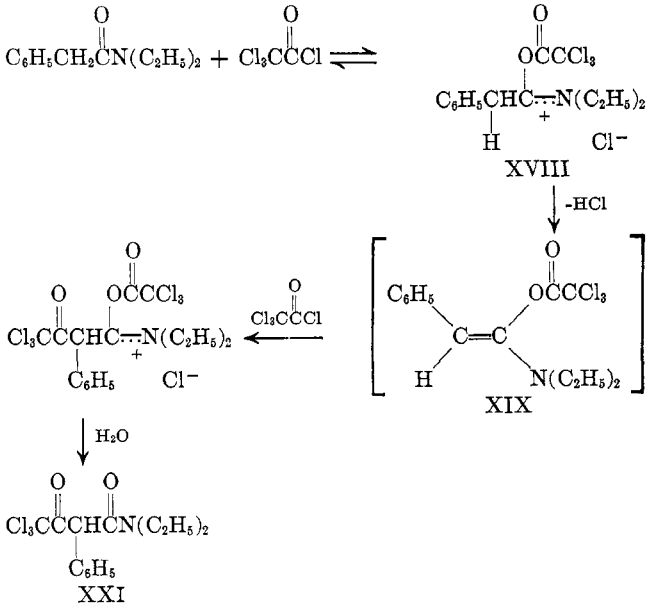


the iodoamide or the iodofuranone amine is an unlikely possibility.

The mechanism of the reaction of oxalyl chloride with N,N-disubstituted amides raises the question as to whether acid chlorides which cannot cause cyclization would react with these amides in a similar fashion.

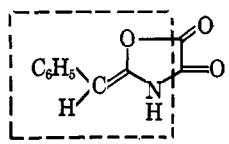
For example, O-acylation of N,N-diethyl-2-phenylacetamide with trichloroacetyl chloride could yield

the enamino ester XIX by loss of hydrogen chloride. Acylation of XIX followed by hydrolysis would produce the acetoacetamide XXI. In fact, treatment of



XXI

N,N-diethyl-2-phenylacetamide with trichloroacetyl chloride in refluxing benzene for 72 hr. did yield N,N-diethyl-2-phenyl-4,4,4-trichloroacetoacetamide (XXI). The n.m.r. spectrum of XXI showed the aromatic protons at τ 2.67 (five protons), the proton on C-2 at 4.25 (singlet, one proton) the methylene protons at 6.68 (multiplet, four protons), and the methyl protons at 8.95 (quartet, six protons). Although this n.m.r. spectrum does not rule out structure XIX for the product, the stability of the product in the presence of aqueous acid makes this structure highly unlikely. The structure XIX is completely ruled out by the compound's failure to absorb in the ultraviolet above 220 mμ. In contrast, the model compound XX shows strong absorption at 240 mμ (log ϵ 4.12) and 330 mμ (log ϵ 4.16).[1]



XX

A small amount of N,N-diethyl-2,2,2-trichloroacetamide was also isolated from this reaction.[2] This new method of preparation of acetoacetic acid derivatives, carried out under acid conditions and with base-sensitive compounds, should be a valuable synthetic method.

Experimental Section[4]

Furanone Amines (II).—Furanone amines were prepared by allowing a substituted acetamide to react with 2 equiv. of oxalyl chloride. The reaction was carried out as follows. The acetamide was dissolved in methylene chloride, and oxalyl chloride in methylene chloride was added dropwise, with stirring, while cooling the solution in an ice bath. The solution was allowed to warm to room temperature and stirred for 1–2 hr., then heated for a short period of time to ensure complete reaction. The resulting furanone amine was crystallized from methylene chloride–hexane. The reactions were carried out on a 0.09–0.20 mole scale. The furanone amines prepared are given in Table I.

(4) Melting and boiling points are uncorrected.

Methyl N,N-Diethyl-2-phenyloxalacetamate (XI).—A mixture of dimethyl oxalate (11.8 g., 0.1 mole), potassium *t*-butoxide (11.2 g., 0.1 mole), and toluene (100 ml.) was stirred while N,N-dimethyl-2-phenylacetamide (19.1 g., 0.1 mole) was added dropwise. The mixture was stirred and refluxed for 1 hr. during which time the solids dissolved and a new solid precipitated. The mixture was poured into ice water (200 ml.), stirred, and acidified to pH 2 with 12 *N* hydrochloric acid. The toluene solution was separated and the aqueous solution was washed with benzene (100 ml.). The toluene and benzene extracts were combined and dried over anhydrous sodium sulfate. The solvents were removed *in vacuo* and recrystallization of the residue from methylene chloride–hexane gave methyl N,N-diethyl-2-phenyloxalacetamate (14.7 g., 0.053 mole, 53%), m.p. 112–113°. *Anal.* Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.55; H, 6.77; N, 5.36.

Reaction of N-Methyl-α-iodoacetanilide with Oxalyl Chloride.—N-Methyl-α-iodoacetanilide (23.4 g., 0.085 mole) was dissolved in methylene chloride; oxalyl chloride (21.6 g., 0.17 mole) was added dropwise (with stirring) while cooling the solution in an ice bath. The ice bath was removed, and the solution was allowed to warm to room temperature and stirred for 0.5 hr. The solution was treated with charcoal, and the solvent was evaporated to a small volume. An oil separated on addition of hexane. The oil in methylene chloride was chromatographed on a column of Woelm neutral alumina, activity grade I. The eluate was evaporated to a small volume. The addition of hexane gave 5-methylanilino-2,2,4-trichloro-3(2H)-furanone (5.8 g., 0.020 mole, 23%), m.p. 146–147° (lit.[2] m.p. 149–150°). The infrared spectrum was identical with that of an authentic sample and there was no depression of mixture melting point.

Reaction of N,N-Diphenyl-1,2-dichlorovinylamine and Oxalyl Chloride.—A solution of N,N-diphenyl-1,2-dichlorovinylamine (13.2 g., 0.05 mole) and oxalyl chloride (7.6 g., 0.06 mole) in benzene (100 ml.) was refluxed for 2 hr. and the benzene was removed *in vacuo*. Recrystallization of the residue from methylene chloride–hexane (with charcoal) gave 5-diphenylamino 2,2,4-trichloro-3(2H)-furanone (14.9 g., 0.042 mole, 84%), m.p. 166–167°. The infrared spectrum was identical with that of an authentic sample.[2]

N,N-Diethyl-2-phenylthionacetamide.—A mixture of N,N-diethyl-2-phenylacetamide (18.8 g., 0.1 mole), phosphorus pentasulfide (22.2 g., 0.1 mole), and toluene (200 ml.) was refluxed for 3 hr. with stirring and filtered, and the toluene was removed *in vacuo*. Distillation of the residue gave a purple oil, b.p. 134–140° (0.4 mm.), which solidified on standing. Recrystallization from benzene–hexane gave N,N-diethyl-2-phenylthionacetamide (4.9 g., 0.023 mole, 23%), m.p. 56–57°. *Anal.* Calcd. for $C_{12}H_{17}NS$: C, 69.51; H, 8.27; N, 6.76; S, 15.47. Found: C, 69.32; H, 7.99; N, 6.90; S, 15.49.

Reaction of N,N-Diethyl-2-phenylthionacetamide and Oxalyl Chloride.—A solution of N,N-diethyl-2-phenylthionacetamide (2.1 g., 0.01 mole) in methylene chloride (75 ml.) was stirred at 0° while oxalyl chloride (2.6 g., 0.02 mole) in methylene chloride (25 ml.) was added dropwise. The solution was stirred for 5 hr. and refluxed for 0.5 hr. The methylene chloride was removed *in vacuo* and the dark brown residue was placed on a column of neutral alumina (Woelm) packed wet with hexane. Elution with benzene gave a crystalline solid. Recrystallization from acetone–water and methylene chloride–hexane gave 5-diethylamino-2,2-dichloro-4-phenyl-3(2H)-furanone (0.94 g., 0.0031 mole, 31%), m.p. 119–120° (lit.[2] m.p. 119–121°). The infrared spectrum (CS_2) was identical with that of an authentic sample and there was no depression of mixture melting point.

Reaction of N,N-Diethyl-2-phenylacetamide with Trichloroacetyl Chloride.—A solution of N,N-diethyl-2-phenylacetamide (17.7 g., 0.1 mole), trichloroacetyl chloride (36.4 g., 0.2 mole), and benzene (100 ml.) was refluxed for 72 hr. Cold water was added and the solution was stirred for 1 hr. The benzene layer was washed with saturated sodium bicarbonate solution (100 ml.) and dried over sodium sulfate. The benzene was evaporated and the solid residue was recrystallized (with charcoal) from methylene chloride–hexane. This gave N,N-diethyl-2-phenyl-4,4,4-trichloroacetoacetamide (XXI, 10.35 g., 0.031 mole, 31%), m.p. 114–116°. *Anal.* Calcd. for $C_{14}H_{16}Cl_3NO_2$: C, 49.95; H, 4.79; Cl, 31.58; N, 4.16. Found: C, 49.69; H, 4.32; Cl, 32.07; N, 4.84.

Distillation of the mother liquor gave N,N-diethyl-2,2,2-trichloroacetamide (2.3 g., 0.01 mole, 10%). The infrared spectrum was identical with that of an authentic sample.