[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MASSACHUSETTS]

Oxidative Reactions of Hydrazines. I. A New Synthesis of Acid Chlorides[1,2]

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A synthesis of acid chlorides has been developed which involves treatment of an acid hydrazide with hydrogen chloride and chlorine.

Acid hydrazides were found by Curtius[3] to be oxidized by iodine to the corresponding diacylhydrazines. The present communication shows that in the presence of an excess of hydrogen chloride, oxidation with chlorine yields the acid chloride.[4] This conversion was first encountered during an examination of synthetic routes to azo compounds having hydrogen attached to one of the doubly-bound nitrogen atoms. Such monosubstituted diimides (RN=NH) have been postulated as intermediates in several reactions but there is little, if any, experimental evidence for their existence.[5] Goldschmidt,[6] on oxidation of *p*-bromophenylhydrazine by means of quinone, obtained a solution which was considered to contain *p*-bromophenyldiimide ($p\text{-}BrC_6H_4N{=}NH$) although the experimental evidence was far from conclusive.

In a preliminary survey of methods which might show promise in the development of syntheses of such compounds or their derivatives, benzyl benzoylazoformate (I) was treated with hydrogen bromide in acetic acid according to the cleavage procedure of Ben-Ishai and Berger.[7] Simple cleavage did not occur, and the product isolated had the composition and properties of a tribromide V. It is postulated that the tribromide is formed by reduction of the azo compound I by hydrogen bromide,

$$\begin{tikzcd}
\underset{\text{I}}{C_6H_5CON{=}NCOOCH_2C_6H_5} \arrow[r, "HBr", "/" marking] \arrow[d, "HBr"'] & \underset{\text{II}}{C_6H_5CON{=}NH_2^+\,Br^-} \\
\underset{\text{III}}{C_6H_5CONHNHCOOCH_2C_6H_5} + Br_2 \arrow[r, "HBr"] & {} \\
\underset{\text{IV}}{C_6H_5CONHNH_3^+\,Br^-} \arrow[r, "Br_2"] & \underset{\text{V}}{C_6H_5CONHNH_3^+\,Br_3^-}
\end{tikzcd}$$

cleavage of the hydrazo compound III to the hydrobromide IV and reaction of IV with the bromine formed in the first step of the reaction. After the initial observation[8] the reaction was never precisely repeated, the difficulty being ascribed to the volatility of the bromine. In support of this postulated course of the reaction, it has been found that benzhydrazidium bromide, upon treatment with bromine, yields a compound with properties similar to those of the substance obtained from the azoformate. The tribromide loses bromine readily to the atmosphere and is insoluble in or decomposed by all solvents which have been examined for attempted purification. Analysis was achieved by determination of the bromine-uptake of weighed samples of the hydrobromide. The molar ratio of bromine to hydrobromide was found to be 0.97 ± 0.04, indicating a 1:1 complex.

Decomposition of V by means of cracked ice yields small amounts of benzoic acid, 1,2-dibenzoylhydrazine and benzhydrazidium bromide whereas if an additional mole of bromine is present during the decomposition there is obtained a 48% yield of benzoyl bromide. In view of the decided increase in stability of trihalides in passing from the trichlorides to the triiodides,[9] both the chloro and iodo analogs of V were examined. The triiodide was found to be relatively stable even in aqueous solution whereas the trichloride could not be obtained. Instead, immediate decomposition to the acid chloride occurred. This decomposition under anhydrous conditions provides a new and novel synthesis of acid chlorides which in most cases is extremely rapid. The reaction shows promise as a general route to these useful intermediates, particularly when the ordinary methods fail or when the esters and thus the hydrazides are more readily available than the acids. Isolation of the desired product is greatly simplified by the fact that the active reagent and all by-products of the reaction are gaseous. Selected acid chlorides which have been prepared by this method are shown in Table I. The reaction is conducted by successively passing hydrogen chloride and chlorine through a solution of the hydrazide in nitromethane. The nitroalkanes proved to be the most generally useful solvents although methylene dichloride was used in a few cases.

When benzyl carbazate hydrochloride (VI) was subjected to treatment with chlorine the expected acid chloride, benzyl chloroformate, was not formed. Instead, benzyl chloride was obtained in 76% yield under conditions (ice-bath cooling) such that the acid chloride, had it formed initially, would be stable toward loss of carbon dioxide.[10]

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[1] This work was supported by grants from the Research Corp., N. Y.

[2] Presented before the 128th National Meeting of the American Chemical Society, Minneapolis, Minn., Sept. 16, 1955. A preliminary communication has appeared in *Chemistry and Industry*, 123 (1955).

[3] T. Curtius, *J. prakt. Chem.*, [2] **50**, 281 (1894).

[4] Certain activated benzenesulfonhydrazides (*m*- and *p*-nitro) have previously been shown to be converted to the sulfonyl chlorides by treatment of the free base with chlorine; W. Davies, F. R. Storrie and S. H. Tucker, *J. Chem. Soc.*, 624 (1931).

[5] See A. Angeli and Z. Jolles, *Ber.*, **62**, 2099 (1929); F. Raschig, *Z. angew. Chem*, **23**, 972 (1910); J. Thiele, *Ann.*, **271**, 127 (1892); F. O. Rice and M. Freamo, THIS JOURNAL, **73**, 5529 (1951); **75**, 548 (1953); L. Kalb and O. Gross, *Ber.*, **59**, 727 (1926); R. Stolle, *ibid.*, **45**, 275 (1912); N. J. Leonard and S. Gelfand, THIS JOURNAL, **77**, 3269, 3272 (1955).

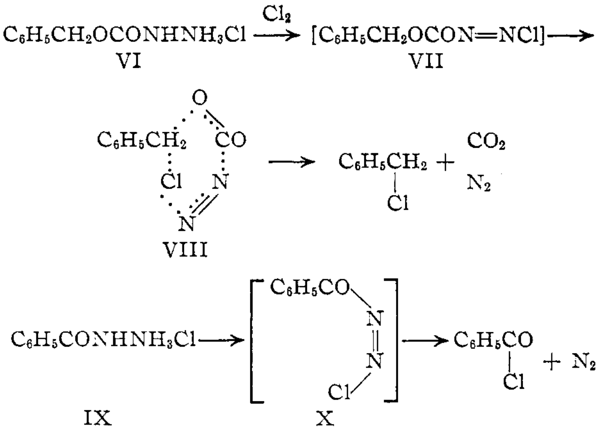
[6] S. Goldschmidt, *Ber.*, **46**, 1529, 2300 (1913).

[7] D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952); *cf.* N. F. Albertson and F. C. McKay, THIS JOURNAL, **75**, 5323 (1953).

[8] Formation of the tribromide was initially observed in the laboratories of Dr. H. R. Snyder at the University of Illinois.

[9] N. V. Sidgwick, "The Chemical Elements and their Compounds," Vol. II, Oxford, 1950, p. 1193.

[10] M. Bergmann and L. Zervas [*Ber.*, **65**, 1192 (1932)] found that



This suggests that an intermediate is involved which decomposes to the alkyl halide rather than the acid chloride because of the special geometry of the carbazate. An intermediate which fits this description is the chloroazo compound VII, the formation of which would be analogous to the conversion of phenylhydrazine to benzenediazonium chloride by the action of chlorine in acidic solution.[11]

Decomposition of the intermediate VII could proceed through the favored six-atom cyclic transition state VIII rather than through a 1,3-shift, ionic process or whatever mechanism might apply in the case of the analogous azo compound X derived from a carboxylic acid hydrazide.

TABLE I[a,f]

Acid chloride	B.p. °C.	Mm.	Method	$n^t\text{D}$	t, °C.	Yield, %
C_6H_5COCl	87–88	25	A	1.5519	22	71.1
$C_6H_5CH_2COCl$	98–99	22	B	1.5317	24	65.6
m-$O_2NC_6H_4COCl$[b]	.....	..	A	....	..	62.5
p-$O_2NC_6H_4COCl$	96–97	0.1	B	....	..	78.9
o-ClC_6H_4COCl	119–120	20	A	1.5714	22	74.0
$(CH_2COCl)_2$	90	20	A	....	..	48.1
$(CH_3)_2CHCOCl$	90–91	..	B[c]	....	..	62.5
n-$C_{11}H_{23}COCl$	143–148	12	A[d]	....	..	66.7
1,4-$C_6H_4(COOCH_3)COCl$	.....	..	A[e]	....	..	78.6

[a] Unless otherwise indicated method A employs nitromethane, method B nitroethane as solvent and prior condensation of the chlorine (see Experimental section). [b] Isolated as amide, m.p. 139.5–140.5° (reported m.p. 141.2°, S. E. Swartz, *Am. Chem. J.*, **19**, 305 (1897)). [c] Methylene dichloride used as solvent. [d] Chloroform or methylene dichloride used as solvent. A large flask is required due to frothing. [e] Isolated as dimethyl terephthalate, m.p. 141–143° (reported m.p. 140.8; M. T. Bogert and C. P. Harris, THIS JOURNAL, **41**, 1676 (1919)). [f] The hydrazides were prepared by standard procedures involving refluxing the ester with hydrazine hydrate.

Experimental[12]

Benzoyl Chloride from Benzhydrazide. Method A.—A solution of 13.6 g. of benzhydrazide dissolved in 200 ml. of warm nitromethane was saturated with dry hydrogen chloride gas and then a stream of dry chlorine was passed through the mixture until the white solid had dissolved completely. This required about 30 minutes, after which the nitromethane was removed by distillation from a water-bath (75°) with the aid of a water aspirator (25 mm.). The yellow liquid (12 g., 85.5%) was distilled through a 30-cm. spiral packed column, b.p. 87–88° (25 mm.), $n^{22}\text{D}$ 1.5519, yield 10.0 g. (71.1%). The anilide was prepared for characterization, m.p. and mixture m.p. 163–164°.

Phenylacetyl Chloride from Phenacethydrazide. Method B.—A solution of chlorine was prepared by passing chlorine gas into 50 ml. of nitroethane which was cooled in a Dry Ice–acetone-bath until 14 g. (0.197 mole) was absorbed. This solution was added all at once to a similarly cooled suspension of phenacethydrazide hydrochloride in 200 ml. of nitroethane prepared from 11.36 g. (0.075 mole) of the hydrazide and dry hydrogen chloride. The mixture was removed from the cooling bath and allowed to stand at room temperature for a few minutes when a vigorous reaction set in and continued for 2–3 minutes. The temperature rose to about 0° and was held at this point by means of the cooling bath until the reaction slowed down. The mixture, which still contained a small amount of the insoluble hydrochloride, was cooled to −10° and chlorine passed in for 2–3 minutes. A clear greenish-yellow solution resulted upon warming to 0° or above and the product was isolated as described above under method A. The yield was 7.61 g. (65.6%), b.p. 98–99° (22 mm.), $n^{24}\text{D}$ 1.5317. The amide was prepared for characterization, m.p. 155–157° (reported[13] m.p. 157°).

Other acid chlorides were prepared similarly as indicated in Table I.

Benzoyl Bromide from Benzhydrazide.—A solution of 13.6 g. (0.1 mole) of benzhydrazide dissolved in 200 ml. of methylene dichloride was saturated with dry hydrogen bromide and then 32 g. (0.2 mole) of bromine was added. An orange mass separated in place of the hydrobromide and after standing for five minutes the mixture was poured onto 200 g. of cracked ice with vigorous stirring. The organic layer was separated and washed rapidly with two 100-ml. portions of ice-cold water and two 100-ml. portions of ice-cold 10% sodium carbonate solution. After drying the solution over anhydrous magnesium sulfate the bromide was isolated as described for the preparation of benzoyl chloride. The yield was 8.9 g. (48.1%), b.p. 48–50° (0.05 mm.), $n^{25}\text{D}$ 1.5868. The bromide was characterized as the addition product with benzaldehyde, m.p. 67–69° (reported[14] m.p. 69–70°).

In one case, when nitromethane was used as the solvent, washing was accompanied by emulsion formation and the only product isolated was benzoic acid (m.p. 122–124°, 81.9% yield). If only one mole of bromine was added prior to decomposition the only products isolated were small amounts of benzoic acid, m.p. 122–124°, 1,2-dibenzoylhydrazine, m.p. 238–240°, and unreacted benzhydrazide hydrobromide, m.p. 215–217°.

Cleavage of Benzyl Benzoylazoformate by Hydrogen Bromide.—The azoformate was prepared as described previously.[15] A solution of 2 g. of the azo compound dissolved in 10 ml. of dry acetic acid was saturated with hydrogen bromide and the flask corked loosely in an attempt to prevent the loss of bromine. A solid soon separated and was filtered and washed with ether. The yield was 0.6 g. of white crystals, m.p. 211–213°. A portion was recrystallized from ethanol-nitromethane (1:1) and had m.p. 215–217°. The melting point was not depressed by admixture with an authentic sample of benzhydrazide hydrobromide. The formation of the hydrobromide in this cleavage was general in wet or dry acetic acid, nitromethane or methylene dichloride as solvents notwithstanding the fact that it was in such a cleavage using ordinary acetic acid in an open vessel that the compound V with its unusual properties was first observed. Dry hydrogen chloride in nitromethane, which does not affect the benzyloxycarbonyl group at ordinary temperatures, reduces the azoformate to the corresponding hydrazo compound III,[15] m.p. and mixed m.p. 154–155°.

Formation of Benzhydrazidium Tribromide V.—A solution of 3.4 g. of benzhydrazide in 25 ml. of nitromethane was saturated with hydrogen bromide and 4.0 g. of bromine was added to the resulting slurry. A yellow-orange amorphous mass took the place of the hydrobromide. The product was washed onto a filter with an additional 100 ml. of nitromethane. It has not been possible to obtain in this way a product free of nitromethane. On standing in the air or

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the acid chloride was stable at temperatures as high as 60°, although attempted distillation gave benzyl chloride.

[11] F. D. Chattaway, *J. Chem. Soc.*, **93**, 852 (1908).

[12] All melting points and boiling points are uncorrected.

[13] W. Braren and E. Buchner, *Ber.*, **34**, 985 (1901).

[14] L. Claisen, *ibid.*, **14**, 2475 (1881).

[15] L. A. Carpino, Ph.D. thesis, University of Illinois, 1953. This work will be published shortly.

in an evacuated but closed vacuum desiccator the compound lost bromine and benzhydrazide hydrobromide (m.p. and mixed m.p. 215–217°) remained. Since purification was not possible the substance was characterized by adding a portion to cracked ice and allowing the reaction to proceed until gaseous evolution stopped. An excess of aniline was then added, the mixture stirred and treated with dilute hydrochloric acid. The resulting solid was recrystallized from ethanol, m.p. 162–164°. The melting point was not depressed on admixture with an authentic sample of benzanilide. For analysis, samples of the hydrobromide were allowed to stand in a desiccator in contact with bromine. Values for the molar ratio of bromine to benzhydrazide hydrobromide ranged from 0.95 to 1.03.

Formation of Benzhydrazidium Triiodide.—A solution of 12.6 g. of iodine in 10 ml. of 47% hydriodic acid was added to a solution of 6.8 g. of benzhydrazide in 20 ml. of 47% hydriodic acid. A bronze-colored solid soon separated. The yield after drying over calcium chloride, potassium hydroxide and ceresin wax was 21 g. (the brown solid became dark green during the drying process). Recrystallization from dilute hydriodic acid gave long bronze needles (9.5 g.), m.p. in a sealed tube 149–153° dec. after the appearance of iodine vapors at 125° and previous softening at 135°. One-gram samples were analyzed roughly by solution in 25 ml. of ethanol and then addition of 100 ml. of 1 *N* sulfuric acid and titration with 0.1 *N* thiosulfate. The results (active I: 45.90, 45.95, 45.82, 46.02%) suggest that the compound is a dihydrate of benzhydrazidium triiodide although it was not obtained sufficiently pure for good elemental analysis.

***p*-Carbomethoxybenzhydrazide.**—A small amount of this compound was the only product isolated in an attempted conversion of a crude sample of dimethyl isophthalate (Brother's Chemical Co., Pract. grade) to isophthalhydrazide by refluxing with hydrazine hydrate. The monohydrazide undoubtedly is derived from dimethyl terephthalate present as an impurity. The hydrazide melted at 204–205.5° after recrystallization from nitromethane–dimethylformamide (1:1).

Anal. Calcd. for $C_9H_{10}O_3N_2$: C, 55.66; H, 5.19. Found: C, 55.62; H, 5.06.

Reaction of Benzyl Carbazate with Hydrogen Chloride–Chlorine. Formation of Benzyl Chloride.—A solution of 13.5 g. of benzyl carbazate[16] in 150 ml. of methylene dichloride was cooled in an ice-bath and saturated with hydrogen chloride. Dry chlorine was then passed into the cold mixture until the solid dissolved (two hours).[17] After removal of the solvent from a water-bath at 60° the benzyl chloride was distilled through a 30-cm. spiral-packed column, b.p. 73–75° (16 mm.), yield 7.85 g. (76.1%). The isothiuronium salt melted at 175.5–177.5°; mixed m.p. with an authentic sample 175.5–177.5°.

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[16] N. Rabjohn, THIS JOURNAL, **70**, 240 (1948).

[17] The reaction was much more rapid (10–15 min.) in nitromethane but isolation of the product was simplified in this case by use of methylene chloride.

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Oxidative Reactions of Hydrazines. II. Isophthalimides. New Protective Groups on Nitrogen[1,2]

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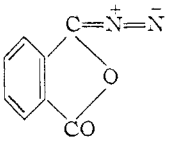
Oxidation of the hydrazones and oximes of phthalaldehydic acid by means of N-bromosuccinimide yields isophthalimides. As an aid in this and other studies new procedures for the selective and rapid removal of protective groups on nitrogen have been developed which involve cleavage of the *t*-butyloxycarbonyl (carbo-*t*-butoxy) group by means of hydrochloric, hydrofluoric or trifluoroacetic acid.

In work directed toward the synthesis of diazophthalide (I), synthetic routes to possible precursors (*e.g.*, V, R = NH_2, OH) were examined. Attempted syntheses of N-aminoisophthalimide (V, R = NH_2) gave either N-aminophthalimide (IV, R = NH_2) or 1,2-phthaloylhydrazine (II). The hydrazone (III, R = $NHCOOCH_2C_6H_5$) obtained from benzyl carbazate and phthalaldehydic acid, on oxidation with N-bromosuccinimide, gave a substance (V, R = $NHCOOCH_2C_6H_5$) isomeric with that (IV, R = $NHCOOCH_2C_6H_5$) obtained from benzyl carbazate and phthalic anhydride. Both isomers were cleaved by hydrogen bromide to N-aminophthalimide, a compound previously obtained from phthalimide and hydrazine.[3]

In view of the facile isomerization of isophthalimides new methods for the removal of protective groups were sought which could be carried out under milder conditions. These methods were originally examined in connection with attempted cleavage of the carbobenzoxy group from benzyl benzoylazoformate ($C_6H_5CON{=}NCOOCH_2C_6H_5$) which underwent reduction of the azo linkage on treatment with hydrogen bromide.[4] Both the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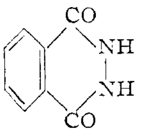
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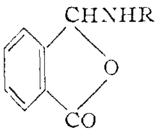
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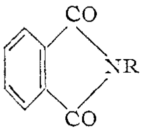
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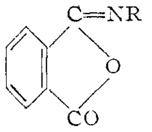
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p-methoxybenzyloxycarbonyl (carboanisoxy) and *t*-butyloxycarbonyl (carbo-*t*-butoxy) groups were found to be cleaved instantaneously at ordinary temperatures by the strong non-reducing acid, trifluoroacetic acid. In the case of the carboanisoxy group difficulties sometimes accompanied separation of the desired product from by-products containing the *p*-methoxybenzyl group. The carbo-*t*-butoxy group did not suffer from such a dis-

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[1] This work was supported by grants from the Research Corporation, New York.

[2] Presented at the 129th National Meeting of the American Chemical Society, Dallas, Texas, April 13, 1956.

[3] H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 16 (1937).

[4] L. A. Carpino, THIS JOURNAL, **79**, 96 (1957).