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[CONTRIBUTION FROM THE ROHM AND HAAS COMPANY, REDSTONE ARSENAL RESEARCH DIVISION]

Peroxytrifluoroacetic Acid. I. The Oxidation of Nitrosamines to Nitramines[1]

BY WILLIAM D. EMMONS

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A number of secondary nitrosamines have been quantitatively oxidized to the corresponding nitramines with peroxytrifluoroacetic acid, a new reagent.

Peroxytrifluoroacetic acid has been found to be a unique reagent for the oxidation of nitrosamines to nitramines and a preliminary report of this work has been published.[2] Indeed this reagent constitutes in some respects the method of choice for laboratory preparation of very pure secondary nitramines.

$$R_2NNO \xrightarrow{CF_3CO_3H} R_2NNO_2$$

Previous methods for synthesis of these compounds include the nitrolysis of dialkyl amides[3] and Wright's chloride-catalyzed nitration of secondary amines.[4] The latter method is an excellent one but it is not completely general, and in some cases purification of the products obtained is tedious. In contrast, the oxidation of nitrosamines to nitramines with peroxytrifluoroacetic acid gives a product of high degree of purity in essentially quantitative yield. Since secondary nitrosamines are readily available from nitrosation of the corresponding amines, a new synthesis of nitramines has been established. Previous attempts to oxidize nitrosamines to nitramines have in some cases been partially successful. Thus dinitroxydiethynitrosamine was converted to dinitroxydiethylnitramine in 32% yield with nitric acid and ammonium persulfate.[4] The oxidation of nitrosamines to nitramines with hydrogen peroxide and nitric acid also has been reported but this procedure also suffers from the relatively low yield of nitramine obtained.[5] The superiority of peroxytrifluoroacetic acid over other reagents for nitrosamine oxidation is certainly dependent on the pronounced electrical dissymmetry of the oxygen–oxygen bond caused by the highly electronegative trifluoroacetyl radical. Thus the reagent is even able to oxidize a weakly nucleophilic species such as nitrosamine, probably through transfer of hydroxyl cation, $OH^{\oplus}$, in the transition state.

Peroxytrifluoroacetic acid may be prepared either by addition of 90% hydrogen peroxide to excess trifluoroacetic acid or from trifluoroacetic anhydride and 90% hydrogen peroxide. The latter procedure is to be preferred, however, since with it an anhydrous solution containing only peroxytrifluoroacetic acid and trifluoroacetic acid may be obtained in a variety of solvents. Methylene chloride has proved to be an exceptionally satisfactory solvent for oxidations with peroxytrifluoroacetic acid.

$$CF_3CO_2H + H_2O_2 \rightleftharpoons CF_3CO_3H + H_2O$$

$$(CF_3CO)_2O + H_2O_2 \longrightarrow CF_3CO_3H + CF_3CO_2H$$

It is interesting to note that there is every indication that the equilibrium between peroxytrifluoroacetic acid and water is established very rapidly. Attempts have been made to determine the equilibrium concentration of peroxytrifluoroacetic acid and hydrogen peroxide present in this system. The procedure used for this was that reported by Greenspan and MacKellar which was developed for the concurrent determination of hydrogen peroxide and peracetic acid.[6] Unfortunately, titration of the hydrogen peroxide in trifluoroacetic acid with ceric ammonium sulfate gave complete recovery of the hydrogen peroxide in every case. Thus it is probable that the equilibrium between hydrogen peroxide and peroxytrifluoroacetic acid is established so rapidly that conventional analytical methods cannot be used to determine equilibrium concentrations.

Some effort has been devoted to a study of the stability of solutions of peroxytrifluoroacetic acid. This work was done primarily to establish the limitations of this reagent as an oxidizing agent so that an intelligent choice of reaction conditions could be made without suffering undue loss of active oxygen by thermal decomposition. Figure 1 represents the results of some of these experiments. Aliquots were removed during each run and the total active oxygen determined by iodometry. It was found that in many cases the decomposition was autocatalytic, and it should be emphasized that the curves are intended only to provide a working knowledge of the stability of peroxytrifluoroacetic acid rather than kinetic data regarding its decomposition. At 25° it was found that a solution of 10 ml. of 90% hydrogen peroxide in 130 ml. of trifluoroacetic acid lost 7% of its active oxygen in 24 hours, 16% in 48 hours and 26% in three days. The most stable solutions were those prepared from trifluoroacetic anhydride and hydrogen peroxide in methylene chloride. Such a solution lost essentially no active

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(1) This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

(2) W. D. Emmons and A. F. Ferris, THIS JOURNAL, **75**, 4623 (1953).

(3) A. H. Lamberton, *Quart. Revs.*, **5**, 75 (1951).

(4) W. J. Chute, K. G. Herring, L. E. Toombs and G. F Wright, *Can. J. Research*, **27B**, 89 (1949).

(5) F. S. Brockman, D. C. Downing and G. F Wright, *ibid.*, **27B**, 69 (1949).

(6) F. P. Greenspan and D. G. MacKellar, *Anal. Chem.*, **20**, 1061 (1948).

oxygen during a reflux period of 24 hours. Thus peroxytrifluoroacetic acid is somewhat more stable than performic acid[7] and certainly represents a very efficient oxidizing agent if used under the proper conditions.

The oxidation of nitrosamines to nitramines was carried out with peroxytrifluoroacetic acid under anhydrous conditions in methylene chloride (procedure A) and also with solutions of 90% hydrogen peroxide in trifluoroacetic acid (procedure B). The experimental results are summarized in Table I. The products were obtained from this oxidation in a high degree of purity and were not contaminated even by traces of nitrosamines. The procedure employing anhydrous peroxytrifluoroacetic acid in methylene chloride is to be preferred over that employing 90% hydrogen peroxide in trifluoroacetic acid since it gives slightly higher yields and somewhat purer products. Furthermore, the reaction is easier to control in methylene chloride since it is run at the reflux temperature of the solvent.

TABLE I

OXIDATION OF NITROSAMINES TO NITRAMINES WITH PEROXYTRIFLUOROACETIC ACID

Nitramine	Yield, % Procedure A	Yield, % Procedure B
Dimethylnitramine	73	77
Methylethylnitramine	80	74
Diethylnitramine	91	76
Dipropylnitramine	95	75
Diisopropylnitramine	90	84
Dibutylnitramine	92	77
N-Nitromorpholine	82	76
N-Nitropiperidine	77	86

In all of the work described above, hydrogen peroxide was employed as the 90% reagent. While there are certain hazards present in the handling of this material, oxidation reactions have been found to go much more smoothly and rapidly with it than with 30% hydrogen peroxide. Thus in the oxidation of N-nitrosopiperidine in trifluoroacetic acid the yield fell from 86 to 53% when 30% hydrogen peroxide was used. Furthermore, some unreacted nitrosamine was present, and the separation of this from the nitramine was tedious.

Acknowledgment.—We are indebted to Dr. K. S. McCallum for obtaining the thermal stability curves of peroxytrifluoroacetic acid and to Dr. R. M. Ross for his encouragement and enthusiasm throughout these investigations.

Experimental

Dialkylnitrosamines.—These compounds were all prepared by action of nitrous acid on the corresponding amines. As a typical example the preparation of diethylnitrosamine is described. To a solution of 110 g. of diethylamine hydrochloride in 100 ml. of water was added 2 ml. of concentrated hydrochloric acid. This solution was then heated to 90° and at this temperature was added dropwise a solution of 76 g. of sodium nitrite in 125 ml. of water. After addition was complete, another 2 ml. of hydrochloric acid was added. The mixture was then heated at 90–95° for one hour. It was cooled and the nitrosamine was extracted with five 100-ml. portions of methylene chloride. The combined extracts were dried over magnesium sulfate and the solvent then removed under reduced pressure. The diethylnitrosamine was distilled to yield 84.0 g. (82%) of clear yellow liquid, b.p. 42° (6.0 mm.), $n^{20}\text{D}$ 1.4378.

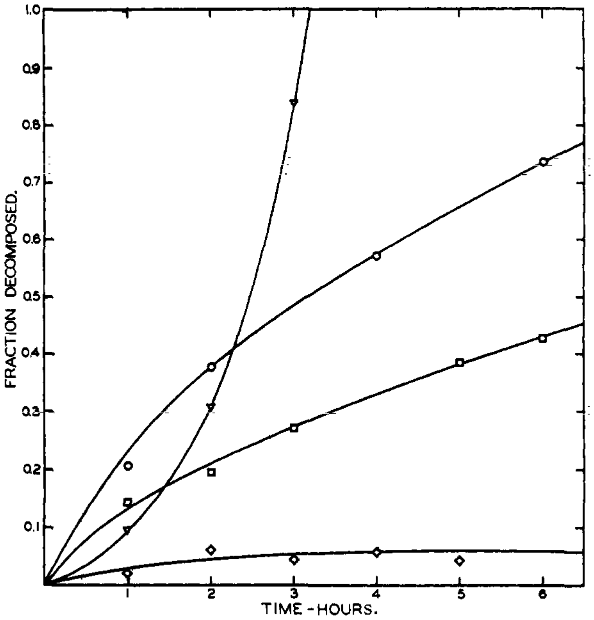

Fig. 1.—Rates of decomposition of hydrogen peroxide-trifluoroacetic acid solutions: ∇, 10 ml. of 90% H_2O_2 + 115 ml. of CF_3COOH at reflux; ◇, 10 ml. of 90% H_2O_2 + 115 ml. of CF_3COOH at 50°; ○, 25 ml. of 30% H_2O_2 + 75 ml. of CF_3COOH at reflux; □, 25 ml. of 30% H_2O_2 + 75 ml. of CF_3COOH at 50°.

Diethylnitramine (Procedure A).—To 4.1 ml. (0.15 mole) of 90% hydrogen peroxide suspended in 100 ml. of methylene chloride with stirring was added in one portion 26 ml. (0.18 mole) of trifluoroacetic anhydride. Since the preparation of peroxytrifluoroacetic acid in this manner is an exothermic reaction, it was most conveniently carried out at ice-bath temperatures. After a five-minute period the solution was allowed to warm to room temperature and 8.1 g. (0.1 mole) of diethylnitrosamine in 10 ml. of methylene chloride was added dropwise over a 30-minute period. During this addition an exothermic reaction was noted which caused the solution to boil. After addition was complete the mixture was heated under reflux for one hour. The methylene chloride was then washed with 100 ml. of water and dried over magnesium sulfate. The solvent was distilled under reduced pressure yielding 8.6 g. (91%) of fairly pure diethylnitramine, $n^{20}\text{D}$ 1.4530. After distillation of this sample there was obtained 7.1 g. (76%) of colorless diethylnitramine, b.p. 48° (0.5 mm.), $n^{20}\text{D}$ 1.4539.

Diisopropylnitramine (Procedure A).—A solution of peroxytrifluoroacetic acid in 100 ml. of methylene chloride was prepared from 4.1 ml. (0.15 mole) of 90% hydrogen peroxide and 26 ml. (0.18 mole) of trifluoroacetic anhydride as described above. To this solution at room temperature was added 13.0 g. (0.1 mole) of diisopropylnitrosamine in 10 ml. of methylene chloride over a 20-minute period. The exothermic reaction caused the solvent to boil vigorously during addition. The solution was then heated under reflux one hour and the volatile solvent distilled under reduced pressure. There was obtained a mushy solid to which was added 25 ml. of cold water. The white crystalline diisopropylnitramine was then collected on a filter and washed with a little water, yield 13.1 g. (90%), m.p. 106–108° (lit. m.p. 108–108.5°[8]).

Dimethylnitramine (Procedure B).—To a solution of 7.4 g. (0.1 mole) of dimethylnitrosamine in 37 ml. of trifluoroacetic acid at 20° was added 4.1 ml. (0.15 mole) of 90% hydrogen peroxide. No change in the temperature of the solution was observed. The mixture was heated with stir-

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(7) D. Swern, *Chem. Revs.*, **45**, 1 (1949).

(8) W. J. Chute, G. E. Dunn, J. C. McKenzie, G. S. Meyers, G. N. R. Smart, J. W. Suggitt and G. F Wright, *Can. J. Research*, **27B**, 114 (1949).

ring to 40° where an exothermic reaction began. The temperature of the solution was maintained at 40–50° for one hour by intermittent cooling with an ice-bath. The mixture was then quenched in 150 ml. of ice-water and the aqueous solution extracted with three 50-ml. portions of methylene chloride. The combined extracts were washed with 10% sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure yielded 6.5 g. (72%) of colorless crystalline dimethylnitramine, m.p. 55–56° (lit. m.p. 57°[4]).

N-Nitromorpholine (Procedure B).—To a solution of 11.6 g. (0.1 mole) of N-nitrosomorpholine in 37 ml. of trifluoroacetic acid was added at 20° with stirring 4.1 ml. (0.15 mole) of 90% hydrogen peroxide. Slight heating with a water-bath was required to initiate the exothermic reaction. The temperature was maintained at 40–50° by intermittent cooling for one hour. The solution was then worked up in the manner described above. There was obtained 10.0 g. (76%) of colorless crystalline N-nitromorpholine, m.p. 52–53° (lit. m.p. 53–54°[8]).

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[CONTRIBUTION FROM THE ROHM AND HAAS COMPANY, REDSTONE ARSENAL RESEARCH DIVISION]

Peroxytrifluoroacetic Acid. II. The Oxidation of Anilines to Nitrobenzenes[1]

BY WILLIAM D. EMMONS

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It has been established that peroxytrifluoroacetic acid is a general reagent for the oxidation of anilines to nitrobenzenes in essentially quantitative yields. The reagent is particularly effective for negatively substituted anilines.

The oxidation of a wide variety of anilines to the corresponding nitrobenzenes has been carried out smoothly in almost quantitative yields with peroxytrifluoroacetic acid. This reaction has in the

$$ArNH_2 \xrightarrow{CF_3CO_3H} ArNO_2$$

past been accomplished with both peroxyacetic acid[2,3] and with Caro's acid,[4,5] but yields of nitrobenzenes obtained generally have been extremely poor. Thus the oxidation of aniline with peroxyacetic acid has been shown by Greenspan to give 11% nitrobenzene and 71% azoxybenzene.[3] The formation of substantial quantities of azoxybenzenes is, in fact, the major disadvantage of oxidation of anilines with peroxyacetic acid. In contrast, the products obtained from peroxytrifluoroacetic acid oxidation were of an excellent state of purity, and no indication of azoxybenzene formation has been observed. The high acidity of the reaction medium is of course responsible for the fact that secondary condensation reactions such as azoxybenzene formation do not occur.

The oxidation of aromatic amines was carried out with peroxytrifluoroacetic acid prepared from trifluoroacetic anhydride and 90% hydrogen peroxide in methylene chloride and also with solutions of 90% hydrogen peroxide in trifluoroacetic acid. The anhydrous reagent in methylene chloride was somewhat more reactive, and oxidation reactions with it usually could be run at a lower temperature. Peroxytrifluoroacetic acid in methylene chloride was also to be preferred since it gave slightly higher yields and a somewhat better grade of product. Furthermore, the reactions were run at the reflux temperature of this solvent and under these conditions were much easier to control. A summary of the experimental investigations may be found in Table I. The yields are in most cases based on the products initially isolated from the reaction but generally these products were fairly pure. The oxidation of *m*- and *p*-phenylenediamine to the corresponding dinitrobenzenes in high yield is particularly noteworthy, and indeed represents the only such examples reported in the literature. N-Methylaniline also was oxidized and was converted to nitrobenzene in excellent yield. As a synthetic method the oxidation of anilines to nitrobenzenes is obviously of value in cases where the nitrobenzene cannot be made by direct nitration of an available starting material. Thus this oxidation is very probably the method of choice for preparation of such compounds as 2,4,6-tribromonitrobenzene, 2,4,6-trichloronitrobenzene and 1,2,4-trinitrobenzene. In general the oxidation of anilines with peroxytrifluoroacetic acid proceeds quite rapidly at the reflux temperature of methylene chloride. In most of the experiments a 30% excess of the peroxyacid over the three equivalents required was used in the reaction.

TABLE I

OXIDATION OF ANILINES TO NITROBENZENES

Aniline	Nitrobenzene	Yield,[a] %
Aniline	Nitrobenzene	89 (79)
N-Methylaniline	Nitrobenzene	84
p-Bromoaniline	*p*-Bromonitrobenzene	90 (85)
p-Chloroaniline	*p*-Chloronitrobenzene	87
o-Nitroaniline	*o*-Dinitrobenzene	92 (81)
m-Nitroaniline	*m*-Dinitrobenzene	86 (92)
p-Nitroaniline	*p*-Dinitrobenzene	94 (86)
m-Phenylenediamine	*m*-Dinitrobenzene	76 (76)
p-Phenylenediamine	*p*-Dinitrobenzene	86 (89)
p-Aminobenzonitrile	*p*-Nitrobenzonitrile	96 (98)
p-Toluidine	*p*-Nitrotoluene	78
o-Toluidine	*o*-Nitrotoluene	71
p-Aminobenzoic acid	*p*-Nitrobenzoic acid	92
Ethyl *p*-aminobenzoate	Ethyl *p*-nitrobenzoate	99
2,4,6-Tribromoaniline	2,4,6-Tribromonitrobenzene	100
2,4,6-Trichloroaniline	2,4,6-Trichloronitrobenzene	98
2-Amino-*p*-cymene	2-Nitro-*p*-cymene	54
2,4-Dinitroaniline	1,2,4-Trinitrobenzene	87

[a] The figures in parentheses represent yields obtained with 90% hydrogen peroxide in trifluoroacetic acid.

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(1) This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

(2) J. D'Ans and A. Kneip, *Ber.*, **48**, 1144 (1915).

(3) F. P. Greenspan, *Ind. Eng. Chem.*, **39**, 847 (1947).

(4) E. Bamberger and F. Tschirmer, *Ber.*, **32**, 1675 (1899).

(5) W. D. Langley, *Org. Syntheses*, **22**, 44 (1942).