

# THE USE OF TRIFLUOROACETIC ANHYDRIDE AND RELATED COMPOUNDS IN ORGANIC SYNTHESSES

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## I. INTRODUCTION

In 1948 an investigation into the properties and derivatives of trifluoroacetic acid was commenced by Stacey, Bourne, Tatlow, and their colleagues at the University of Birmingham, England. In the course of this work a sample of cellulose which had been swollen in acetic acid was treated with trifluoroacetic anhydride. The product of this reaction was normal cellulose acetate, and no trifluoroacetyl group had been introduced. As a result of this a general study of

the condensing properties of trifluoroacetic anhydride was begun by Stacey and his colleagues. This work, and subsequent investigation by many other laboratories, has shown that trifluoroacetic anhydride has many applications as a condensing agent in organic syntheses.

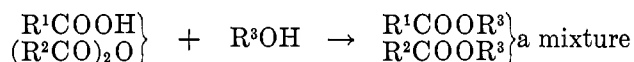
The use of anhydrides of strong acids to promote condensations of weaker acids is by no means a recent development. Phosphoric anhydride was used to condense carboxylic acids with aromatic nuclei as far back as 1872. The use of carboxylic anhydrides is more recent, although the ability of monochloroacetic anhydride to promote the acylation of cellulose by weaker carboxylic acids was known some twenty years before the discovery that trifluoroacetic anhydride would do the same. Monochloroacetic anhydride has also been used to condense carboxylic acids with anisole to form ketones, and there are many other reports of one carboxylic anhydride promoting acylation by a different carboxylic acid. For most of these reactions, the use of trifluoroacetic anhydride offers a far more effective condensing agent.

It is the object of this review to describe condensations promoted by carboxylic anhydrides in general and by trifluoroacetic anhydride in particular. Considerable attention has been devoted to the mechanism of the condensations and to the properties of mixed anhydrides. A brief consideration is also given to some other uses of trifluoroacetic acid. Finally an account of the methods for preparing and handling trifluoroacetic acid and its anhydride is given. The literature has been surveyed up to October 1954, although some later work is included, thanks to authors who made their manuscripts available to the reviewer prior to publication.

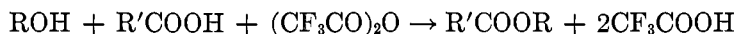
## II. ESTERIFICATION

### A. THE USE OF TRIFLUOROACETIC ANHYDRIDE TO PROMOTE ESTERIFICATION (SEE TABLE 1)

It has been known for many years that if an alcohol is treated with a mixture of a carboxylic acid and the anhydride of a different carboxylic acid, esters of both acids are prepared.



The proportion of each ester depends on the strength and steric properties of the two acids concerned. Except for the preparation of mixed esters of cellulose (59, 61, 78), this reaction has little value, unless it can be performed so that the proportion of one ester greatly exceeds the proportion of the other, to the point of yielding almost exclusively one ester. This is what happens when a hydroxy compound is treated with a solution of a carboxylic acid in trifluoroacetic anhydride (39, 190).



When this reaction is used as a general method for the preparation of simple esters, the carboxylic acid (approximately 1 mole) is dissolved in trifluoroacetic

TABLE 1  
*Esterifications promoted by trifluoroacetic anhydride*  
 $A \cdot OH + ROH + (CF_3CO)_2O \rightarrow RO \cdot A + 2CF_3COOH$

| Acid<br>(A·OH)  | Hydroxy Compounds<br>(ROH)   | Ester<br>(RO·A)  | Yield              | Reference |
|---|--|--|--------------------|-----------|
| Acetic.....   | <i>p</i> -Nitrobenzyl alcohol  | <i>p</i> -Nitrobenzyl acetate  | 83                 | (39)      |
|   | D-Mannitol   | Mannitol hexaacetate   | 80                 | (39)      |
|   | Sucrose  | Sucrose octaacetate  | 67                 | (39)      |
|   | $\alpha, \alpha$ -Trehalose  | Trehalose octaacetate  | 68                 | (39)      |
|   | Methyl $\alpha$ -D-glucopyranoside   | Methyl 2, 3, 4, 6-tetra- <i>O</i> -acetyl- $\alpha$ -D-glucopyranoside   | 56                 | (39)      |
|   | Methyl 4, 6- <i>O</i> -benzylidene 3- <i>O</i> -trifluoroacetyl- $\alpha$ -D-glucopyranoside | Methyl 2- <i>O</i> -acetyl-4, 6- <i>O</i> -benzylidene-3- <i>O</i> -trifluoroacetyl- $\alpha$ -D-glucopyranoside | 64                 | (38)      |
|   | $\beta$ -Naphthol  | $\beta$ -Naphthyl acetate  | 85                 | (39)      |
|   | Cellulose  | Cellulose triacetate   | (Acetyl,<br>40-42) | (39)      |
|   | Amylose  | Amylose triacetate   | (Acetyl,<br>41.6)  | (39)      |
|   | Propionic.....   | Polyvinyl alcohol  | Polyvinyl acetate  |           |
| Methyl $\alpha$ -D-glucopyranoside  |  | Methyl 2, 3, 4, 6-tetra- <i>O</i> -propionyl- $\alpha$ -D-glucopyranoside  | 77                 | (39)      |
| Maltose   |  | $\alpha$ -Maltose octapropionate   | 28                 | (39)      |
| Palmitic.....   | $\beta$ -Naphthol  | $\beta$ -Naphthyl propionate   | 68                 | (39)      |
|   | Glycerol   | Glyceryl tripalmitate  | 70                 | (39)      |
| Acrylic.....  | $\beta$ -Naphthol  | $\beta$ -Naphthyl palmitate  | 85                 | (39)      |
|   | 1,1-Difluorobutyl alcohol  | 1,1-Difluorobutyl acrylate   | 85-90              | (1)       |
| Benzoic.....  | Phenol   | Phenyl acrylate  | 56                 | (1)       |
|   | <i>p</i> -Nitrobenzyl alcohol  | <i>p</i> -Nitrobenzyl benzoate   | 69                 | (39)      |
|   | Ethylene glycol  | Ethylene dibenzoate  | 48                 | (39)      |
|   | D-Mannitol   | Mannitol hexabenzoate  | 41                 | (39)      |
|   | 2, 3, 4, 6-Tetra- <i>O</i> -acetyl- $\beta$ -D-glucose                                       | 2, 3, 4, 6-Tetra- <i>O</i> -acetyl-1- <i>O</i> -benzoyl- $\beta$ -D-glucose                                      | 9-12               | (208)     |
| Benzoic.....  | Methyl 4, 6- <i>O</i> -benzylidene-3- <i>O</i> -trifluoroacetyl- $\alpha$ -D-glucopyranoside | Methyl 2- <i>O</i> -benzoyl-4, 6-benzylidene-3- <i>O</i> -trifluoroacetyl- $\alpha$ -D-glucopyranoside           | ?                  | (35)      |
|   | Phenol   | Phenyl benzoate  | 82                 | (39)      |
|   | $\beta$ -Naphthol  | $\beta$ -Naphthyl benzoate   | 80                 | (39)      |
| Phenylacetic.....   | Cellulose  | Cellulose benzoate   | (Benzoyl,<br>60)   | (39)      |
|   | <i>p</i> -Nitrobenzyl alcohol  | <i>p</i> -Nitrobenzyl phenylacetate  | 64                 | (39)      |
| Cinnamic.....   | $\beta$ -Naphthol  | $\beta$ -Naphthyl phenylacetate  | 61                 | (196)     |
|   | Methyl alcohol   | Methyl cinnamate   | 46                 | (196)     |
| Succinic.....   | $\beta$ -Naphthol  | $\beta$ -Naphthyl succinate  | 15                 | (196)     |
| Adipic.....   | Phenol   | Phenyl adipate   | 64                 | (39)      |
| Phthalic.....   | <i>p</i> -Nitrobenzyl alcohol  | —  | 0                  | (196)     |
| <i>p</i> -Toluenesulfonic.....  | $\beta$ -Naphthol  | $\beta$ -Naphthyl <i>p</i> -toluenesulfonate   | 13                 | (39)      |
| Nitric.....   | D-Mannitol   | Mannitol hexanitrate   | 45                 | (41)      |
|   | D-Sorbitol   | Sorbitol hexanitrate   | 45                 | (41)      |
| Hydroxy Acids and Related Compounds   |  |  |                    |           |
| 1,2- <i>O</i> -Isopropylidene-3- <i>O</i> -[2,2'-diphenyldicarboxylic acid ester]-D-glucufuranose |  | 1,2- <i>O</i> -Isopropylidene-3,5- <i>O</i> -[2,2'-diphenoyl]-D-glucufuranose                                    | 60                 | (181)     |
| 2'-Hydroxybibenzyl-2-carboxylic acid.....   |  | Lactone  | 95                 | (13)      |
| 2-Carboxy-2'-hydroxybenzophenone.....   |  | Lactide  | 32                 | (10)      |
| 2-Carboxy-2'-hydroxy-5'-methylbenzophenone.....   |  | Lactone  | 49                 | (10)      |
| 2-Carboxy-2'-hydroxydiphenylmethane.....  |  | Lactone  | 75                 | (10)      |
| 2-Carboxy-2'-hydroxy-5'-methyldiphenylmethane.....  |  | Lactone  | 99                 | (10)      |
| <i>p</i> -Hydroxybenzoic acid.....  |  | Linear polymer   |                    | (39)      |
| Salicylic acid.....   |  | Mixture of tetra- and hexa-salicylides   |                    | (11)      |
| Thiosalicylic acid.....   |  | Mixture of <i>cis</i> -di-, tri-, and tetrathiosalicylides   |                    | (11)      |
| Riboflavin-5'-phosphate.....  |  | Riboflavin-4',5'-cyclophosphate  | 100                | (99)      |
| Adenylic acid.....  |  | Adenosine-2',3'-phosphate  |                    | (44)      |
| Cytidylic acid.....   |  | Cytidine-2',3'-phosphate   |                    | (44)      |
| Uridylic acid.....  |  | Uridine-2',3'-phosphate  |                    | (44)      |

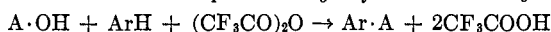
anhydride (1.2–1.5 moles) (solvation is usually rapid but in some cases gentle warming may be necessary), and the alcohol (1 mole for a monohydric compound, 0.5 mole for a dihydric compound, etc.) is added to the anhydride solution. For the simplest acids and alcohols the reaction is spontaneous and very rapid, but with less reactive acids and hydroxy compounds gentle warming is required to complete the esterification. Primary, secondary, and tertiary alcohols, polyhydroxy alcohols, phenols, and thiophenols have all been esterified by this reaction. In general, less reactive hydroxy compounds give better yields of the desired ester than do the most reactive primary alcohols (such as methanol). This is because small yields of the trifluoroacetate ester are formed with these reactive alcohols, whereas with phenols the desired esterification can be nearly quantitative.

A great variety of carboxylic acids can be esterified by this method, the chief limitation being that of acid strength. Thus the strongest acids (e.g., monochloroacetic acid,  $K_a = 1.5 \times 10^{-3}$ ; 3,4-dinitrobenzoic acid,  $K_a = 1.6 \times 10^{-3}$ ) cannot be satisfactorily esterified by this method. Dibasic acids can be esterified, provided they do not preferentially form stable cyclic anhydrides; thus adipic acid gives a good yield of ester (39), whereas succinic acid does not (196). Hydroxy acids either form lactones (10, 11, 13) if these are sterically favored, or else they form linear polyesters (39). The reaction has also been applied to the preparation of hexitol nitrates from nitric acid (41), of a phenol tosylate from *p*-toluenesulfonic acid (39), and of various phosphoric acid derivatives (36, 44, 99).

The great value of this method of esterification lies in the mild conditions which are required. The stability of acid-labile groups to trifluoroacetic anhydride solutions is well demonstrated by the fact that sucrose octaacetate can be prepared in good yield by this method (39). The method is very convenient for the preparation of polysaccharide esters (39), and it has been shown that the acetylation of bacterial cellulose by a solution of acetic acid in trifluoroacetic anhydride causes very little degradation (17). The stability of unsaturated molecules is shown by the preparation of monomeric esters which normally polymerize in the presence of strong acids (1, 2). Thus phenyl acrylate has been prepared in good yield directly from phenol and acrylic acid, using trifluoroacetic anhydride (1).

The field in which the mild nature of the trifluoroacetic anhydride method has attracted the greatest interest is that of synthetic carbohydrate chemistry. Methyl 4,6-*O*-benzylidene-2-*O*-trifluoroacetyl- $\alpha$ -D-glucopyranoside is readily converted into methyl 2-*O*-trifluoroacetyl-3-*O*-acetyl-4,6-*O*-benzylidene- $\alpha$ -D-glucopyranoside by a solution of acetic acid in trifluoroacetic anhydride. In this reaction the cyclic acetal and the very labile trifluoroacetyl group are unaffected, whereas acetylation by acetic anhydride in pyridine results in the apparent migration and subsequent removal of the trifluoroacetyl group (43). Treatment of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose with a solution of benzoic acid in trifluoroacetic anhydride yields either 1-*O*-benzoyl- $\beta$ -D-glucopyranose tetraacetate or a mixture of the  $\alpha$  and  $\beta$  derivatives, according to the conditions (208). The method has also been used in the preparation of 3,5-*O*-di-

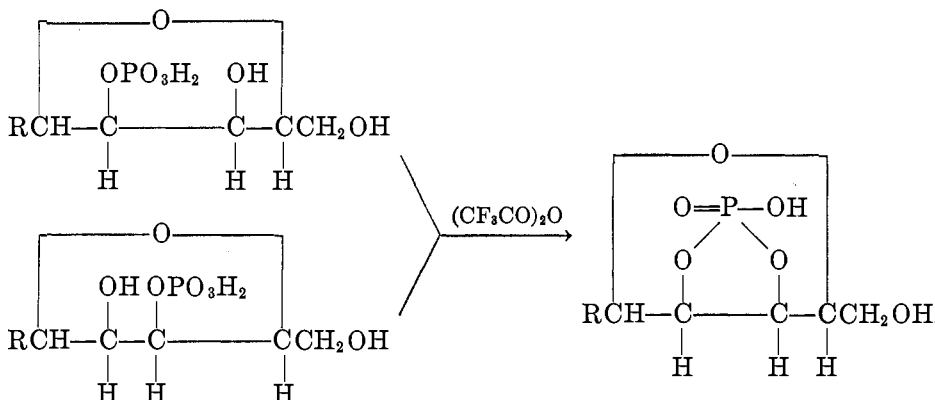
TABLE 2

*Aromatic substitutions promoted by trifluoroacetic anhydride*

| Acid<br>A·OH                            | Aromatic Nucleus<br>ArH    | Product<br>Ar·A                                 | Yield                         | Reference  |       |
|---|----------------------------|---|-------------------------------|------------|-------|
|   |                            |   | <i>per cent</i>               |            |       |
| Acetic.....                             | Anisole                    | <i>p</i> -Methoxyacetophenone                   | 82                            | (40)       |       |
|   | Phenetole                  | <i>p</i> -Ethoxyacetophenone                    | 88                            | (40)       |       |
|   | <i>o</i> -Xylene           | 2,4-Dimethylacetophenone                        | 9                             | (196)      |       |
|   | $\psi$ -Cumene             | 2,4,6-Trimethylacetophenone                     | 6                             | (196)      |       |
|   | <i>m</i> -Xylene           | 2,4-Dimethylacetophenone                        | 5                             | (196)      |       |
|   | Toluene                    | <i>p</i> -Methylacetophenone ?                  | Trace                         | (196)      |       |
|   | Thiophene                  | 2-Acetylthiophene                               | 50                            | (40)       |       |
|   | Furan                      | 2-Acetylfuran                                   | 39                            | (40)       |       |
|   | Benzoic.....               | Mesitylene                                      | 2,4,6-Trimethylbenzophenone   | 51         | (40)  |
|   |                            | Anisole   | <i>p</i> -Methoxybenzophenone | 56         | (40)  |
| Cinnamic.....                           | Anisole                    | 4-Methoxychalcone                               | 64                            | (196)      |       |
| Adipic.....                             | Mesitylene                 | 1,4-Dimesitylbutane                             | 16                            | (196)      |       |
| Hydrocinnamic.....                      | —                          | 1-Hydrindone                                    | 30                            | (88)       |       |
| $\gamma$ -Phenylbutyric.....            | —                          | $\alpha$ -Tetralone                             | 70                            | (88)       |       |
| <i>p</i> -Toluenesulfonic.....          | Anisole                    | <i>p</i> -Methoxyphenyl <i>p</i> -tolyl sulfone | 46                            | (40)       |       |
|   | Mesitylene                 | Mesityl <i>p</i> -tolyl sulfone                 | 64                            | (40)       |       |
| Nitric.....                             | Nitrobenzene               | <i>m</i> -Dinitrobenzene                        | 65                            | (41)       |       |
|   | Bromobenzene               | <i>p</i> -Nitrobromobenzene                     | 24                            | (41)       |       |
|   |                            | <i>o</i> -Nitrobromobenzene                     | 1                             |            |       |
|   |                            | 2,4-Dinitrobromobenzene                         | 60                            |            |       |
| Nitrous.....                            | Phenyl cyanide             | <i>m</i> -Nitrophenyl cyanide                   | 85                            | (41)       |       |
|   | Mesitylene                 | Mesitylenediazonium salt                        | 47                            | (41)       |       |
|   | $\psi$ -Cumene             | 2,4,6-Trimethylbenzenediazonium salt            | 13                            | (41)       |       |
| Hypobromous.....                        | Anisole                    | <i>p</i> -Methoxybenzenediazonium salt          | 21                            | (41)       |       |
|   | Bromobenzene               | Bromobenzene                                    | 89                            | (111)      |       |
|   | Iodobenzene                | <i>p</i> -Bromiodobenzene                       | 85                            | (111)      |       |
|   | Bromobenzene               | <i>p</i> -Dibromobenzene                        | 65                            | (111)      |       |
|   | Chlorobenzene              | <i>p</i> -Bromochlorobenzene                    | 58                            | (111)      |       |
|   | Toluene                    | <i>p</i> -Bromotoluene                          | 73, 91                        | (111, 124) |       |
|   | $\beta$ -Methylnaphthalene | $\alpha$ -Bromo- $\beta$ -methylnaphthalene     | 77                            | (124)      |       |
|   | Anisole                    | <i>p</i> -Bromoanisole                          | 76                            | (111)      |       |
|   | Aniline                    | <i>p</i> -Bromoaniline                          | 62                            | (111)      |       |
|   | Nitrobenzene               | <i>m</i> -Bromonitrobenzene                     | 19                            | (111)      |       |
|   | Benzoic acid               | <i>m</i> -Bromobenzoic acid                     | 61                            | (111)      |       |
|   | Hypoiodous.....            | Benzene   | Iodobenzene                   | 85         | (111) |
|   |                            | Iodobenzene                                     | <i>p</i> -Diiodobenzene       | 6          | (111) |
| <i>p</i> -Diiodobenzene                 |                            |   | 77                            |            |       |
| Bromobenzene                            |                            | <i>p</i> -Bromiodobenzene                       | 71                            | (111)      |       |
| Chlorobenzene                           |                            | <i>p</i> -Chloriodobenzene                      | 62                            | (111)      |       |
| Toluene                                 |                            | <i>p</i> -Iodotoluene                           | 84, 88                        | (111, 124) |       |
| Anisole                                 |                            | <i>p</i> -Iodoanisole                           | 75                            | (111)      |       |
| Aniline                                 |                            | <i>p</i> -Iodoaniline                           | 51                            | (111)      |       |
| <i>N,N</i> -Dimethylaniline             |                            | <i>p</i> -Iodo- <i>N,N</i> -dimethylaniline     | 41                            | (111)      |       |
| Benzoic acid                            |                            | <i>m</i> -Iodobenzoic acid                      | 84                            | (111)      |       |
| 1,2,3,4-Tetrahydrofluoranthene          |                            | 1,2,3,4-Tetrahydro-5-iodofluoranthene           | 75                            | (21)       |       |
| 2-Methyl-1,2,3,4-tetrahydrofluoranthene |                            | 1,2,3,4-Tetrahydro-5-iodo-2-methylfluoranthene  | 74                            | (21)       |       |
| 3-Methyl-1,2,3,4-tetrahydrofluoranthene |                            | 1,2,3,4-Tetrahydro-5-iodo-3-methylfluoranthene  | 71                            | (21)       |       |

phenoyl-D-glucofuranose, by condensing intramolecularly the half-ester of 2,2'-diphenyldicarboxylic acid and 1,2-*O*-isopropylidene-D-glucofuranose. The particularly interesting feature of this reaction is the fact that the ester is formed on the No. 5 carbon atom (i.e., a secondary hydroxyl group) and not on

the No. 6 carbon atom (a primary hydroxyl group). Probably the 6-position reacts initially with the trifluoroacetic anhydride to form an *O*-trifluoroacetyl derivative (*cf.* the above discussion on the reactivity of primary, secondary, and tertiary alcohols), forcing the subsequent intramolecular reaction to take place at the less reactive 5-position (181). A somewhat different example of intramolecular condensation is the preparation of cyclic phosphates. Todd and his coworkers have used trifluoroacetic anhydride to prepare a variety of nucleotide cyclic phosphates (44, 99).



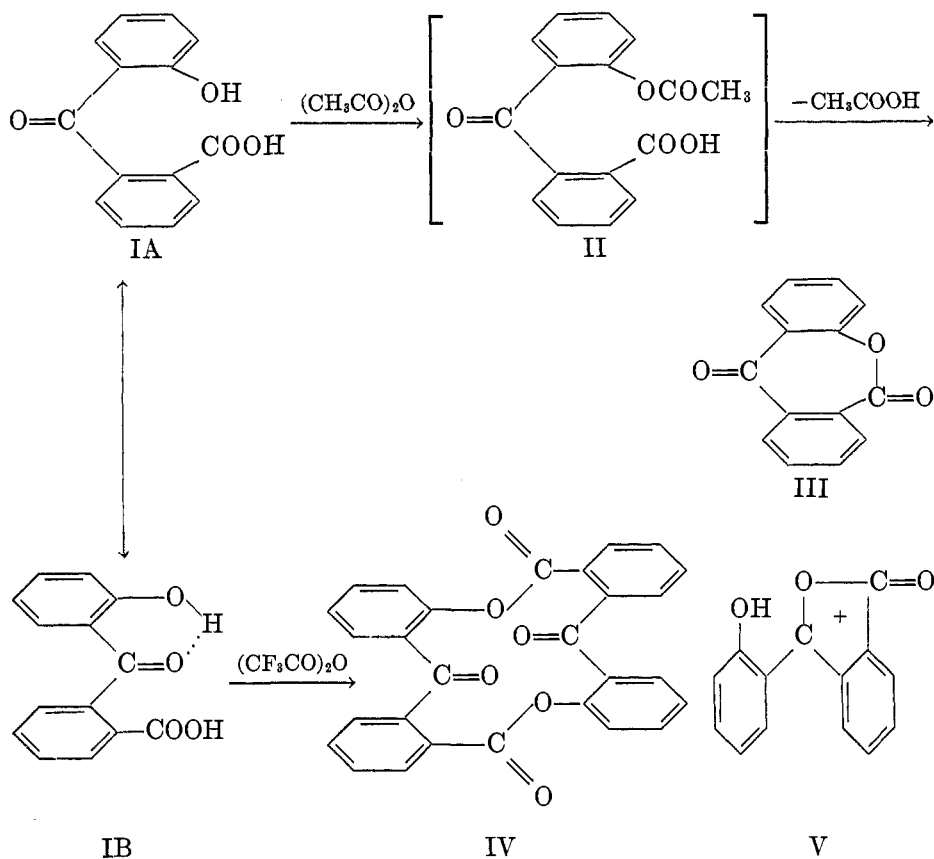
The use of trifluoroacetic anhydride as a condensing agent in esterification finds application in reactions where an unstable or valuable acid is to be condensed with an unreactive or labile hydroxy compound. The fact that the preparation of nearly fifty different esters has been described in over a dozen separate scientific communications shows that the reaction is much more than a chemical curiosity. But trifluoroacetic anhydride is by no means the only acid anhydride to have been used as a condensing agent for esterification. Although no other anhydride has been found so effective or as generally applicable as trifluoroacetic anhydride, it is worth briefly considering the condensing properties of other anhydrides and comparing their reactions with those of trifluoroacetic anhydride.

#### B. THE USE OF ORGANIC ANHYDRIDES OTHER THAN TRIFLUOROACETIC ANHYDRIDE TO PROMOTE ESTERIFICATION

Acetic anhydride, the cheapest and most readily obtained carboxylic acid anhydride, is frequently used in condensation reactions, but its use for preparing esters other than acetates is limited. Under certain circumstances, however, it is possible to use acetic anhydride as a condensing agent to prepare high-boiling esters of other acids. Thus, if phenol, stearic acid, and acetic anhydride are refluxed and then acetic acid slowly bled off, phenyl stearate is present in the residue in good yield (54). Presumably a mixture of phenyl acetate and phenyl stearate is formed initially, in which the former ester probably predominates, but as the acetic acid is removed by distillation, so it is replaced

by transesterification until all the stearic acid is esterified and only the high-boiling ester remains. Obviously this reaction is limited to high-boiling esters which are stable under these very vigorous conditions. In such circumstances it is an extremely satisfactory method of preparation and has been used to prepare esters of  $\alpha$ -phenethylphenol (100).

Acetic anhydride has also been used to promote intramolecular esterification and the preparation of aromatic lactones. In these reactions acetic anhydride sometimes gives a different product from that given by trifluoroacetic anhydride.



When 2-carboxy-2'-hydroxybenzophenone (IA and IB) is treated with acetic anhydride the final product is the seven-membered lactone III, but treatment with trifluoroacetic anhydride (and anhydrides of other strong acids) gives the fourteen-membered lactide IV (12). Wilson Baker and his colleagues suggest that the formation of the lactide is due to intramolecular hydrogen bonding which causes the molecule to take up the configuration IB. They explain the exceptional behavior when acetic anhydride is used by suggesting that the *O*-acetyl derivative II is first formed, which then loses acetic acid by basic cataly-

sis to yield the lactone III. The great objection to this theory is that it implies that acetic anhydride would react with the *o*-hydroxy group, whereas the far more reactive trifluoroacetic anhydride would not. An alternative explanation would be that both anhydrides react initially with the hydroxy acid to form a mixed anhydride. In the acetic anhydride system, this unsymmetrical anhydride then reacts intramolecularly to form III. With trifluoroacetic anhydride and other strong acid anhydrides, the unsymmetrical anhydride ionizes to form ion V, which is known to be particularly stable (166, 168). The same workers also found that acetic anhydride reacts with 2'-hydroxybibenzyl-2-carboxylic acid to yield the *O*-acetyl derivative, while trifluoroacetic anhydride converts it into the lactone (13). These reactions probably also go through the unsymmetrical anhydride. 2-Hydroxyphenylacetic acid treated with acetic anhydride does not give the lactone, but either the *O*-acetyl phenylacetic anhydride or 2-methyl-3-carboxycoumarone, depending on the conditions (170). It would be interesting to investigate the behavior of this compound in trifluoroacetic anhydride.

The anhydrides of both monochloroacetic acid and trichloroacetic acid will promote esterification in a similar manner to trifluoroacetic anhydride. Neither of these compounds is as effective as trifluoroacetic anhydride; they require more vigorous conditions and yield less pure products. There are several patents relating to the use of monochloroacetic anhydride to promote the synthesis of fatty acid esters of cellulose (58, 63, 66, 67, 130, 131, 132, 133, 143). Besides those describing the esterification of cellulose itself, there are patents describing the esterification of partly nitrated cellulose (60, 64) and of partly acetylated cellulose (62, 65, 156). In all these a strong acid is recommended in addition to the "impelling" chloroacetic anhydride. Unfortunately the patents give no real estimation of the amount of chloroacetylation that takes place, nor do they give any account of the extent of degradation.

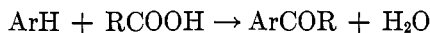
Recently, there has been a description of the use of methanesulfonic anhydride as a condensing agent in ester synthesis (90). At present, only two esterifications employing this compound have been reported. Since methanesulfonic acid is a very much stronger acid than trifluoroacetic, its anhydride may well prove a more effective condensing agent than trifluoroacetic anhydride. In particular, it may be capable of esterifying relatively strong acids which cannot be condensed by trifluoroacetic anhydride. On the other hand, the very fact that it is a stronger acid makes it less suitable for reactions involving labile molecules and it has been found unsuitable for promoting the acetylation of sucrose.

### III. ELECTROPHILIC SUBSTITUTION OF AROMATIC COMPOUNDS

(SEE TABLE 2)

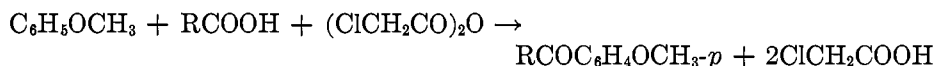
#### A. SYNTHESIS OF KETONES

Acid anhydrides have for many years been used to promote the condensation of carboxylic acids with aromatic compounds.



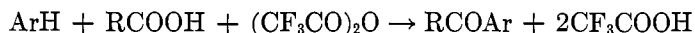


Phosphorus pentoxide was first used for this reaction in 1872 (144). Benzophenone was synthesized in fair yield by heating benzene and benzoic acid with phosphorus pentoxide at 180–200°C. for 5 hr. Later several substituted benzophenones were prepared similarly (145). Much more recently the same anhydride has been used to prepare ketones from aliphatic acids and activated aromatic compounds (e.g., phenol ethers and polyalkylbenzenes) under relatively mild conditions (146). The first real use of an organic anhydride for this type of condensation seems to have been made in 1933, when Unger published a paper describing the acylation of anisole by mixtures of carboxylic acids and anhydrides (201). Twenty different ketones were prepared by heating various carboxylic acids with anisole and monochloroacetic anhydride (in the proportions 1:1:2, respectively) for 48 hr. at 170–180°C. Yields varied from a trace to over 90 per cent. *o*-Nitrobenzoic anhydride proved quite ineffective and only very poor yields of ketone were obtained when the same reaction was attempted

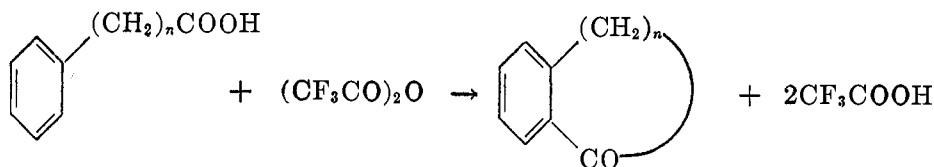


with phthalic anhydride.

The use of trifluoroacetic anhydride instead of monochloroacetic anhydride for the synthesis of ketones enables much milder conditions to be used, and this reaction has been investigated as a potential general method (40). The aromatic compound (1 mole) is added to a solution of the carboxylic acid (1–1.5 moles)



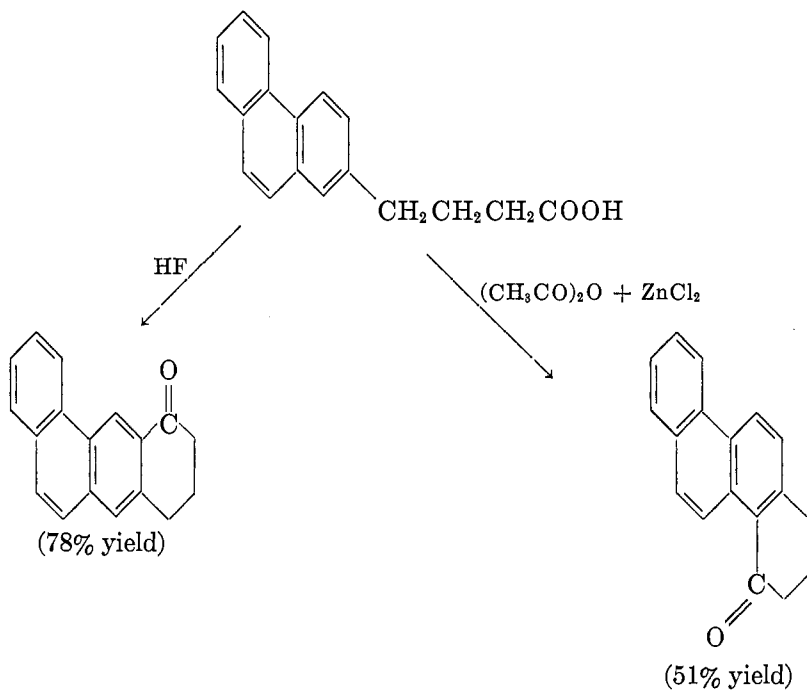
in trifluoroacetic anhydride (1.5–2.5 moles). In most cases the reaction is spontaneous, but in practice it is usually accelerated by gentle warming. The types of aromatic compounds that can be acylated by this reaction are limited. The aromatic nucleus must be activated, and the most suitable compounds include polyalkylbenzenes, phenol ethers, and "superaromatic" heterocyclic compounds such as furan and thiophene. As with the ester synthesis, the choice of the carboxylic acid which can be condensed by trifluoroacetic anhydride is limited by acidic strength. Suitable acids, when treated with trifluoroacetic anhydride, undergo intramolecular condensation to yield cyclic ketones (88).  $\gamma$ -Phenyl-



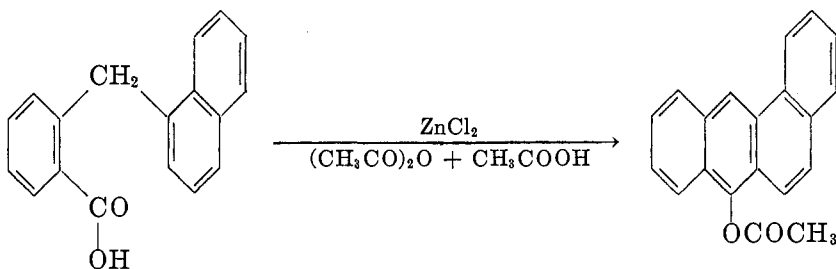
butyric acid ( $n = 3$ ) can be converted into  $\alpha$ -tetralone in good yield by this method, but only poor yields of 1-hydrindone are obtained from hydrocinnamic acid ( $n = 2$ ). Slightly higher yields of 1-hydrindone can be obtained by refluxing hydrocinnamic acid with heptafluorobutyric anhydride (b.p. 107°C.) (88), while prolonged heating (170°C. for 48 hr.) with monochloroacetic anhydride gives a very good yield (201).

Although acetic anhydride cannot be used to promote intermolecular acyla-

tion by other carboxylic acids, it has been used, usually in conjunction with a Lewis acid catalyst, to promote intramolecular condensations (91, 94, 95, 179). The particularly interesting feature of this method lies in the fact that it sometimes gives a different ketone from that given by cyclization with hydrogen fluoride (95; *cf.* also 91).



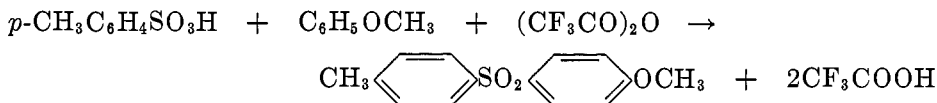
In cyclizations where the resulting ketone will enolize readily, the enol acetate is prepared (68, 69, 92, 93). This derivative is more stable than the free ketone and its preparation can be advantageous (92). These condensations are usually



completed by refluxing the mixture for an hour. However, more vigorous conditions appear to be required if the Lewis acid is omitted, and these have been obtained by using higher-boiling propionic anhydride and also by using acetic anhydride in a sealed tube (20).

## B. SYNTHESIS OF SULFONES

The preparation of aromatic sulfones by condensing arylsulfonic acids with activated aromatic hydrocarbons in the presence of trifluoroacetic anhydride is exactly analogous to the ketone synthesis described above (40). Good yields

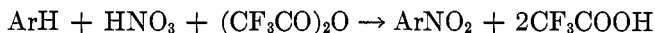


were obtained by this process, better in fact than those previously reported for the conventional Friedel-Crafts reaction, using sulfonyl chloride and aluminum chloride. It is perhaps surprising that acids as strong as arylsulfonic acids should be condensed so readily by trifluoroacetic anhydride (*cf.* Section VI). With esterifications promoted by trifluoroacetic anhydride, strong acids, and *p*-toluenesulfonic acid in particular, were found to give poor yields of ester, presumably because of competing trifluoroacetylation. In the synthesis of ketones and sulfones no trace of trifluoroacetyl acylation has been observed. No other carboxylic anhydrides appear to have been used for this reaction.

## C. NITRATION

A great variety of solvents has been used for the nitration of aromatic nuclei by nitric acid. This choice has been largely empirical, and indeed until recently there have been few theoretical concepts to guide a chemist in selecting the most suitable solvent for a particular nitration. Originally Benford and Ingold (27) divided solvents used for nitration into three groups: "slow" (to include dioxane, acetic acid, and acetonitrile), "medium" (to include nitromethane and acetic anhydride), and "fast" (originally only sulfuric acid). More recently Hughes, Ingold, and Reed (125) have found it more convenient to divide the solvents simply into "slow" (including all solvents originally classed as "intermediate") and "fast" (to include nitric acid itself as well as sulfuric acid).

The use of trifluoroacetic anhydride as a solvent for low-temperature nitrations has proved most effective (41).

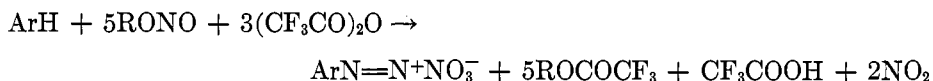


Trifluoroacetic anhydride definitely belongs to the category of "fast" solvents. Deactivated molecules, like nitrobenzene and bromobenzene, warmed at 45–55°C. with approximately equimolar proportions of fuming nitric acid and trifluoroacetic anhydride gave 65 per cent yields of *m*-dinitrobenzene and 2,4-dinitrobenzene, respectively (41). For the nitration of such molecules, trifluoroacetic anhydride has no advantage over sulfuric acid, but for the nitration of acid-labile compounds the anhydride may prove valuable. An example of such a compound is phenyl cyanide. This compound, warmed with fuming nitric acid and trifluoroacetic anhydride at 55°C. for 90 min., gave an 85 per cent yield of *m*-nitrophenyl cyanide, while treatment with a similar solution of nitric acid in sulfuric acid gave a mixture of *m*-nitrophenyl cyanide (40 per cent) and *m*-nitrobenzoic acid (45 per cent) (41).

The use of acetic anhydride as a "slow" solvent for the nitration of reactive aromatic compounds has been very widespread. The advantages of this solvent over possible alternatives is hard to assess. It appears that dinitrogen pentoxide is the principal nitrating agent in this medium (67). The nature of the nitrating agent in trifluoroacetic anhydride will be discussed later (cf. Section VI).

#### D. NITROSYLATION LEADING TO THE FORMATION OF DIAZONIUM SALTS

The preparation of aromatic nitroso compounds by direct electrophilic substitution is possible only with phenols and tertiary amines. When it was attempted to extend this reaction to the nitrosylation of benzenoid hydrocarbons by using solutions of alkyl nitrites in trifluoroacetic anhydride, the desired nitroso derivatives were not obtained. Instead the reaction products consisted of nitro compounds, diazonium salts, and unidentified nitrogenous compounds. With less reactive hydrocarbons (e.g., benzene and naphthalene) nitration predominated, but with activated aromatic compounds (e.g., mesitylene,  $\psi$ -cumene, and anisole) diazonium salts were obtained (41).

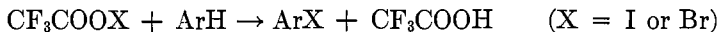


Probably nitroso compounds were formed initially, but these reacted with the nitrous acid or nitric oxide present to yield diazonium salts by well-known reactions (14, 15, 16, 137, 164). Consistent with such a mechanism is the conversion of aryl nitroso compounds into diazonium salts by treatment with solutions of alkyl nitrites in trifluoroacetic anhydride (41). However, the nitro compounds formed in these reactions are almost certainly produced by direct nitration by some powerful nitrating agent (e.g.,  $\text{N}_2\text{O}_5$  or even  $\text{NO}_2^+$ ), rather than by oxidation of initially prepared nitroso compounds.

This reaction provides almost the only method at present known for the direct introduction of a diazonium group into an aromatic hydrocarbon. 2-Hydroxy-5-methylbenzenediazonium nitrate has been prepared directly from *p*-cresol by treatment with aqueous nitrous acid (171), but no hydrocarbon appears to have been diazotized in this way previously. Unfortunately the scope of the reaction appears to be very limited, and it seems unlikely that it will ever have a very wide application. Other carboxylic anhydrides have not been used in this type of condensation.

#### E. HALOGENATION

The use of trifluoroacetyl hypohalites as halogenating agents (21, 111, 124) is not actually a condensing reaction of trifluoroacetic anhydride. However, the process is so closely connected with the true anhydride condensations that its mention here seems fully justified.



The trifluoroacetyl hypohalites are prepared by adding the stoichiometric amount of bromine or iodine to a solution of silver trifluoroacetate in an organic solvent. Carbon tetrachloride appears to be the most suitable solvent (21, 124), although nitrobenzene has also been used (111). In many cases the hydrocarbon to be halogenated can be used as solvent for the whole reaction. The bromination and iodination of reactive compounds, such as toluene, is entirely spontaneous, and in fact external cooling may be necessary. Less reactive compounds require heating.

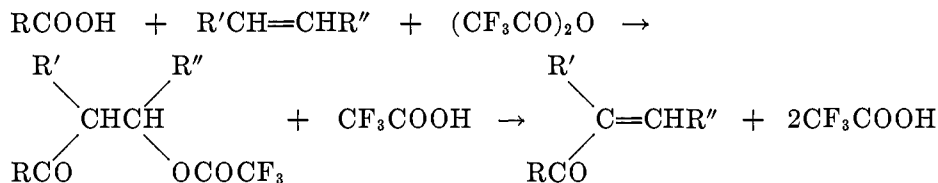
This method of halogenation is really the same as that described by Waters and his coworkers (18, 75, 76), who used the silver salts of strong mineral acids (especially silver sulfate) together with elementary bromine or iodine and a small quantity of concentrated sulfuric acid. Waters' method is somewhat more vigorous than the hypohalite reaction, and nitrobenzene can be iodinated using silver sulfate (18), but not by using silver trifluoroacetate (111). On the other hand the mildness of the trifluoroacetate method may in certain cases be an advantage, and the solubility of silver trifluoroacetate in organic solvents will contribute to the smoothness of the reaction.

Other acyl hypohalites are not very effective. Acetyl hypoiodite gives a poor yield of iodotoluene from toluene, and trichloroacetyl derivatives are quite impractical because of their instability (124).

#### IV. ACYL-ADDITION TO UNSATURATED COMPOUNDS (SEE TABLE 3)

##### A. THE SYNTHESIS OF KETO OLEFINS

When an olefin such as cyclohexene is introduced into a solution of a carboxylic acid in trifluoroacetic anhydride, a spontaneous reaction occurs. The initial product of this reaction is a  $\beta$ -trifluoroacetoxy ketone (I), but these compounds are unstable and readily lose trifluoroacetic acid to yield a 1-keto olefin (II) (120).



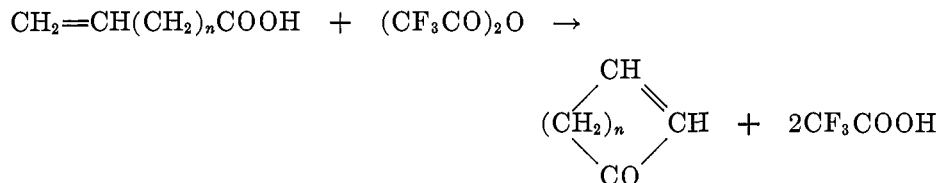
When this reaction is used as a general method for the preparation of keto olefins, the olefin is added directly to a solution of the carboxylic acid in trifluoroacetic anhydride. The reactants are left at room temperature for 2 to 12 hr., depending on the compounds involved, and the whole mixture is then poured into aqueous sodium carbonate, which rapidly releases the free keto olefin; the trifluoroacetic acid may be recovered from the mother liquor.

This method of preparation must be compared with the conventional Friedel-Crafts synthesis, in which the olefin is treated with an acyl chloride and a Lewis acid, followed by the dehydrochlorination of the intermediate product with a tertiary amine (72). The use of trifluoroacetic anhydride dispenses with the preparation of the acid chloride and the overall yields are better (178).

TABLE 3  
*Acyl-addition promoted by trifluoroacetic anhydride*

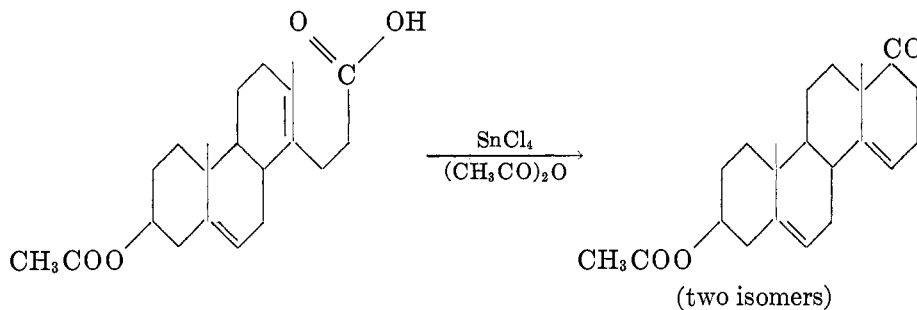
| Acid                    | Unsaturated Compound | Product                    | Yield           | Reference |
|-------------------------|----------------------|----------------------------|-----------------|-----------|
|                         |                      |                            | <i>per cent</i> |           |
| Acetic.....             | Cyclohexene          | Cyclohexenyl methyl ketone | 48              | (120)     |
|                         | 1-Hexene             | 3-Octen-2-one              | 23              | (120)     |
|                         | 1-Pentyne            | 2,4-Heptanedione           | 22              |           |
|                         | 1-Hexyne             | 2,4-Octanedione            | 20              | (120)     |
| Butyric.....            | Cyclohexene          | Cyclohexenyl propyl ketone | 51              | (120)     |
| Benzoic.....            | 1-Hexyne             | 1-Phenyl-1,3-dioxoheptane  | 17              | (120)     |
| Allylaetic.....         | —                    | 2-Cyclopenten-1-one        | 5               | (120)     |
| $\delta$ -Hexenoic..... | 1-Hexyne             | 2-Cyclohexen-1-one         | 45              | (88)      |
| $\delta$ -Hexynoic..... | —                    | 1,3-Cyclohexanedione       |                 | (88)      |
| Nitrous.....            | Cyclohexene          | 1-Cyclohexanol-2-one       |                 | (118)     |

The reaction can be applied to the preparation of cyclic ketones by the intramolecular condensation of suitable olefinic acids (88).



Good yields of ketone are obtained when  $n = 3$ , but when  $n = 2$  considerable polymerization occurs.

Although cyclizations of this type can be achieved by direct condensation using strong acid catalysts under very vigorous conditions (172), they are normally performed via the acid chloride, using a Friedel-Crafts method. In some cases acetic anhydride together with a strong acid catalyst can be used to promote direct intramolecular condensations in a similar manner to trifluoroacetic anhydride. Thus acetic anhydride and stannic chloride have been used to synthesize ring D in a total steroid synthesis (30).



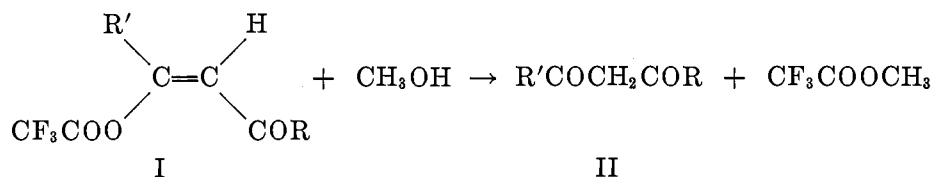
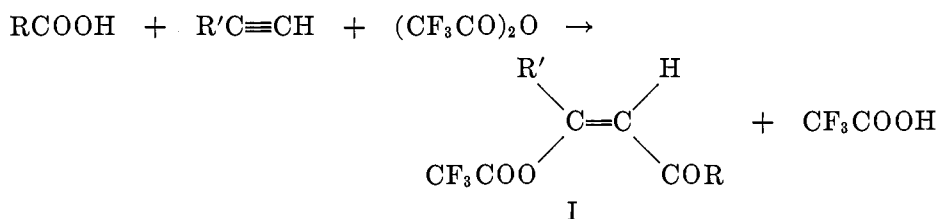
Similarly, acetic anhydride and sulfuric acid have been used to prepare cyclic ketones from aliphatic terpene acids (149).

Acetic anhydride cannot be used to promote the intermolecular condensation

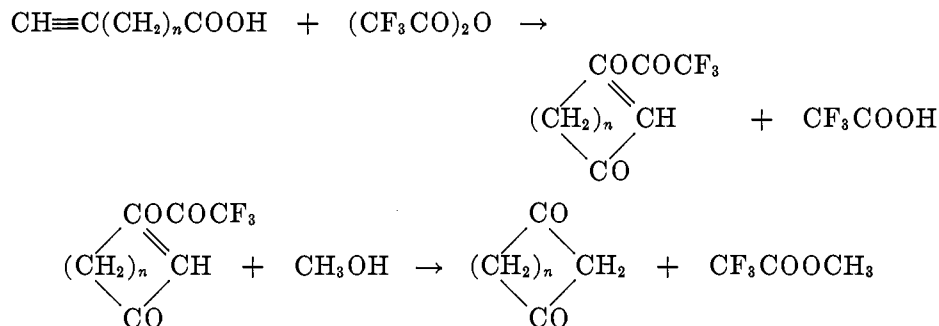
of other carboxylic acids with olefins. Anhydrides of strong carboxylic acids, other than trifluoroacetic anhydride, have not been investigated for this reaction.

#### B. THE SYNTHESIS OF $\beta$ -DIKETONES

The direct addition of carboxylic acids to acetylenes, with the formation of vinyl esters, is well known. However, if the carboxylic acid is first dissolved in trifluoroacetic anhydride and then treated with an acetylene, acyl-addition occurs to yield the enol trifluoroacetate of a  $\beta$ -diketone (I), by a reaction exactly analogous to the synthesis of keto olefins described above. The primary addition product in this case is quite stable and can be readily converted into the free  $\beta$ -diketone by transesterification (120).



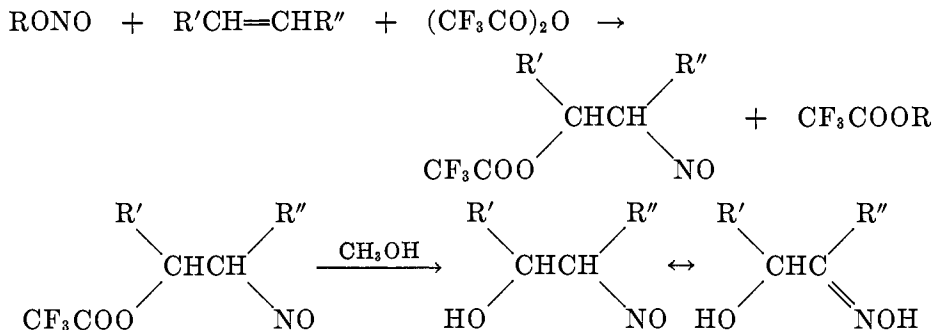
To prepare  $\beta$ -diketones the acetylene is added to a solution of the carboxylic acid in trifluoroacetic anhydride, and the reaction is allowed to take place spontaneously at room temperature. When the addition is judged complete, the reaction mixture is poured into excess methanol. Transesterification of the enol trifluoroacetate is very rapid, and the free ketone is obtained by fractionation. The yields so far reported are low (ca. 20 per cent), but the method provides an entirely new route to these important compounds. Like the synthesis of keto olefins, this reaction can be applied to the intramolecular cyclization of suitable acetylenic acids (88).



At present this reaction has been completed only for  $n = 3$ . Other carboxylic anhydrides have not been used to promote these additions to acetylene.

### C. THE SYNTHESIS OF $\alpha$ -HYDROXY OXIMES

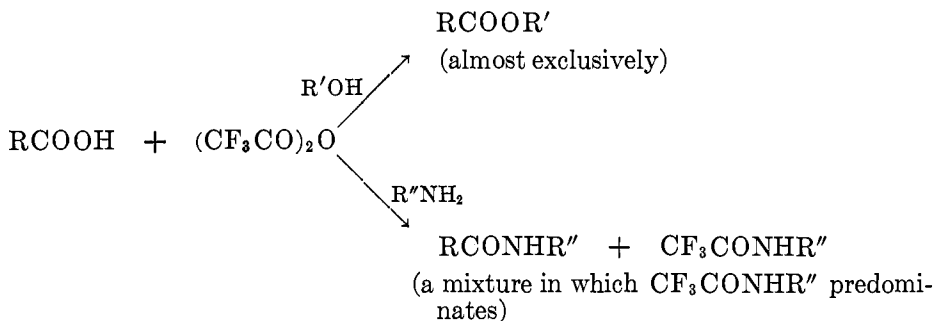
Clearly the addition reactions promoted by trifluoroacetic anhydride described above could be extended to other oxy acids, just as the esterification and aromatic substitution reactions were extended. So far only one such extension has been reported, and that is the acyl-addition of nitrous acid to olefins (119).



## V. OTHER CONDENSATION REACTIONS

### A. CONDENSATIONS INVOLVING BASIC SUBSTANCES

When a primary amine is introduced into a solution of a carboxylic acid in trifluoroacetic anhydride, instead of yielding exclusively the acyl derivatives of the solute acid, as in the ester synthesis, a mixture of amides is produced in which the trifluoroacetyl derivative predominates (34, 37).



The difference between the reaction with alcohols and the reaction with amines can definitely be attributed to the basic properties of the latter compounds. Thus the introduction of basic salts, or even neutral sodium trifluoroacetate, into a solution of a carboxylic acid in trifluoroacetic anhydride inhibits the esterification reaction, and a mixture of esters derived from both the solute acid and trifluoroacetic acid is produced (36).

These facts make trifluoroacetic anhydride unsuitable as a condensing agent to promote *N*-acylation in a manner similar to the *O*-acylations and *C*-acylations

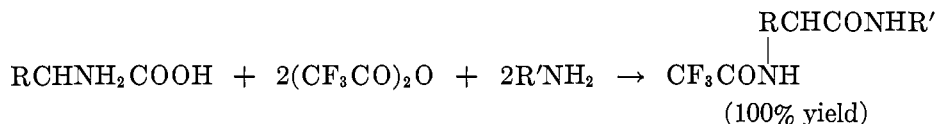


already described. It should also be noted that the *O*- and *C*-acylations are likely to be inhibited by the presence of basic groups in any of the molecules taking part in the condensation. The probable effect that basic substances have on trifluoroacetic anhydride systems will be discussed in Section VI.

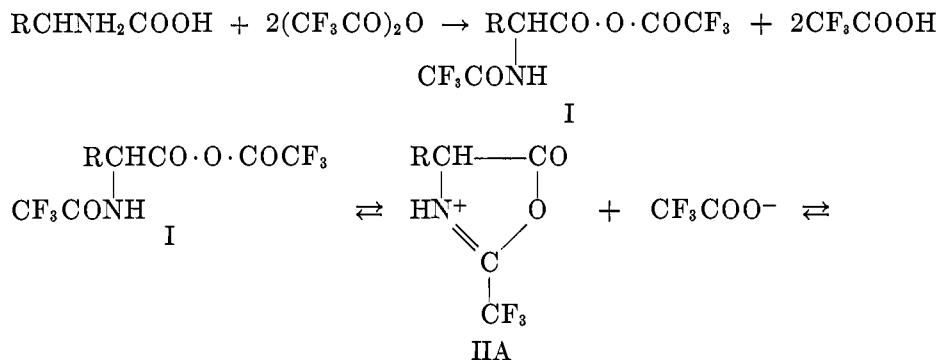
There is one exception to the general failure of trifluoroacetic anhydride as a condensing agent in *N*-acylation reactions. Weygand and Leising have reported that derivatives of  $\alpha$ -amino acid amides can be formed in trifluoroacetic anhydride (207), and since this reaction is definitely different from the behavior of other carboxyl derivatives, the reactions of amino acids in trifluoroacetic anhydride will be dealt with separately.

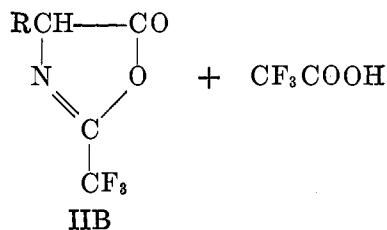
#### B. AMINO ACIDS IN TRIFLUOROACETIC ANHYDRIDE

When an amino acid is treated with a molecular equivalent of trifluoroacetic anhydride, the *N*-trifluoroacetyl derivative is prepared in good yield (205). These derivatives are crystalline and slightly stronger acids than their hydrocarbon analogs. Weygand and Leising (207) report that when an  $\alpha$ -amino acid is treated with 2 moles of trifluoroacetic anhydride, followed by 2 moles of a primary amine, the *N*-trifluoroacetyl amino acid amide is prepared in nearly quantitative yield.



These results appear to be in direct contradiction to the reports of earlier workers described in the previous section. However, if these exceptional results are substantiated, an explanation may be found in azlactone formation. When an  $\alpha$ -amino acid is treated with excess trifluoroacetic anhydride it will first be converted into the *N*-trifluoroacetyl derivative; this will then react with more anhydride to yield the unsymmetrical anhydride (I). It seems likely that the unsymmetrical anhydride will then spontaneously be converted into the azlactone derivatives (IIA and IIB). This compares with the behavior of the *N*-benzoyl amino acid chlorides (52).



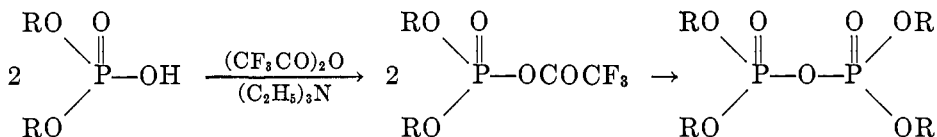


If this azlactonization does occur, then the azlactone (IIA or IIB) would be expected to react with amines to give *N*-trifluoroacetyl amino acid amides, whereas the unsymmetrical anhydride (I) would be expected to give principally trifluoroacetyl derivatives. Some evidence that azlactones are formed in these solutions is provided by Weygand and Leising's observation that *l*-alanine is racemized by trifluoroacetic anhydride (207). *l*-Glutamic acid is converted by trifluoroacetic anhydride into *N*-trifluoroacetylglutamic acid anhydride without racemization (207).

Whether or not azlactones are formed in these solutions, the racemization limits the value of this method for preparing amino acid amides and dipeptides. It does not, of course, detract from the value of *N*-trifluoroacetyl residues as blocking groups in polypeptide synthesis, particularly as these derivatives can now be prepared from ethylthiol trifluoroacetate without recourse to trifluoroacetic anhydride (180).

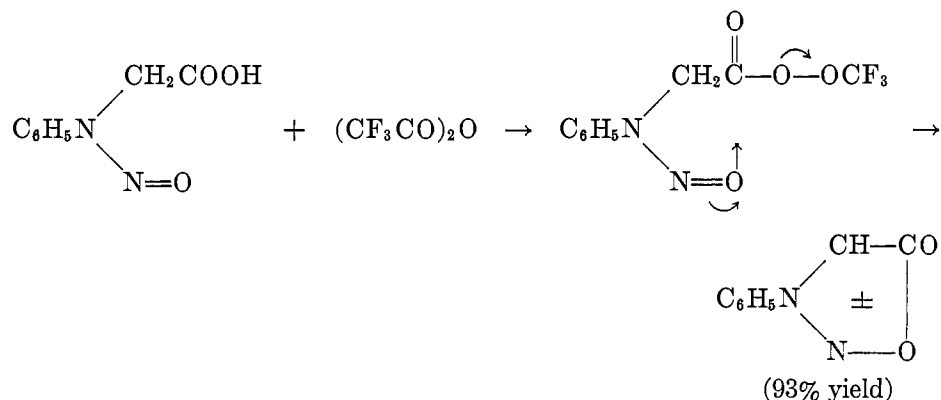
### C. MISCELLANEOUS CONDENSATIONS

The original suggestion that unsymmetrical anhydrides occur in trifluoroacetic anhydride systems (39) has led to the use of this compound for two preparations that were previously known to proceed through an unsymmetrical anhydride molecule. The most important of these preparations is the synthesis of pyrophosphates (70). Thus, dibenzyl hydrogen phosphate in acetonitrile solution treated with triethylamine, followed by trifluoroacetic anhydride, gave a 75 per cent yield of tetrabenzyl pyrophosphate. The use of trifluoroacetic anhydride for this type of reaction was found to provide a particularly mild method.



The second preparation of this type arose out of an investigation into the structure and properties of the Sydnone, when evidence was obtained that the usual preparation of these compounds proceeds via an unsymmetrical anhydride. On this account it was predicted that trifluoroacetic anhydride would prove a more effective condensing agent than acetic anhydride, which had

previously been used, because of the powerful electrophilic effect of the  $\text{CF}_3$  group. This prediction was fully realized (12).



## VI. MECHANISM OF THE CONDENSATION REACTIONS

### A. "MIXED ANHYDRIDE" SYSTEMS<sup>1</sup>

#### 1. General properties of mixed anhydrides

Literature on mixed anhydrides (see footnote 1) goes back over a century, but some of the work is contradictory and most of it is confused. Mixed anhydrides were first prepared by Gerhardt and by Chiozza by treating the sodium salt of one acid with the acid chloride of another (55, 56, 57, 103, 104, 105), and this remains the most important method of preparation. An early modification was the treatment of the silver salt of one acid with the acid chloride of another in ether solution (147), a method which has recently proved useful in the preparation of mixed anhydrides of amino acids for the synthesis of polypeptides (210, 211). Later workers prepared mixed anhydrides by treating various acids with acetic anhydride (4, 5, 6); by mixing two symmetrical anhydrides together (22, 25); by treating the solution of one acid in a tertiary base, with the acid chloride of another acid (77, 142, 200) [this method has also recently been used in connection with peptide syntheses (32, 203)]; and by treating the sodium salt of a monoacyl sulfonate ( $\text{RCOSO}_2\text{ONa}$ ) with the sodium salt of a different carboxylic acid (161, 162, 163). Ketene has been used extensively in more recent times to prepare mixed anhydrides of acetic acid (106, 108, 127, 129), and  $\beta$ -benzoylacrylic acid mixed anhydrides have been

<sup>1</sup> Considerable confusion has arisen in the literature through the failure of workers to be sufficiently precise when discussing reactions of molecules of the type  $\text{RCO}\cdot\text{O}\cdot\text{COR}'$ , which have variously been called "mixed anhydrides," "asymmetric anhydrides," and "unsymmetric anhydrides." In an attempt to clear up some of this confusion the following terms will be employed throughout this discussion: "unsymmetrical anhydride" to refer only to the actual molecule  $\text{RCO}\cdot\text{O}\cdot\text{COR}'$ ; "mixed anhydride" to refer to any system which analyzes for  $\text{RCO}\cdot\text{O}\cdot\text{COR}'$  but which may contain equimolecular mixtures of the two symmetrical anhydrides  $(\text{RCO})_2\text{O}$  and  $(\text{R}'\text{CO})_2\text{O}$  or a mixture of these together with the unsymmetrical anhydride.

prepared from  $\gamma$ -phenylallylacetic acid via an intermediate  $\beta$ -iodo- $\gamma$ -lactone (33, 53).

The earliest workers fully realized that the unsymmetrical anhydride which was initially prepared disproportionated readily into the two symmetrical anhydrides (103). Yet it is almost certainly this reaction which has caused so much of the work reported to be contradictory (*cf.* 109 and 153; 5, 6, and 23; 23 and 177). Rousset doubted the very existence of unsymmetrical anhydrides, because he was able to show that previously described mixed anhydride solutions could be readily separated into two symmetrical anhydrides simply by repeated fractionation (177). The preparation of crystalline mixed anhydrides with fixed melting points at first sight provides a sure method of isolating true unsymmetrical compounds, and many such derivatives have been reported (4, 8, 33, 53, 79, 138, 174, 194, 214). However, Van der Haar provided evidence that at least one such compound [*p*-(*N,N*-dimethylamino)benzoic acetic anhydride, *cf.* 4] was in fact a symmetrical anhydride with a molecule of acetic anhydride of crystallization (202). Evidence that acetic benzoic anhydride was similarly a molecular compound is far less convincing. There are only two completely satisfactory methods for distinguishing between unsymmetrical anhydrides and mixtures of anhydrides. These are kinetic experiments (141, 204) and determinations of the infrared absorption spectra (45). A true unsymmetrical anhydride, on hydrolysis, will give a constant rate constant, experimentally found to be between that of the two symmetrical anhydrides (204), whereas a mixture of the two symmetrical anhydrides will give a decreasing rate "constant" as the symmetrical anhydride which hydrolyzes the most rapidly is consumed. The second and slightly less certain method for identifying the presence of unsymmetrical anhydrides depends on the observation of infrared absorption bands which are characteristic of different anhydrides and which can probably be attributed to the stretching frequency of the ether oxygen atom.

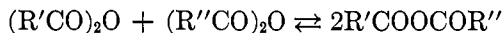
The earliest workers made few attempts to study the reactions of the mixed anhydrides which they had prepared beyond observing that the anhydrides disproportionated and that they could be hydrolyzed by alkali to their constituent acids. The controversies of Autenrieth (5, 6, 7) and Béhal (22, 23, 24, 25) first focussed attention on the reaction of mixed anhydrides with alcohols and amines. Autenrieth reported that his mixed anhydrides reacted with phenylhydrazine and with aniline to give the acyl derivative of the carboxylic acid with the *greatest* number of carbon atoms (5). Béhal, performing similar experiments, reported exactly the reverse (23, 25). He also extended his investigations to the reactions of mixed anhydrides with ethanol, and reported that both esters were prepared, but that the ester derived from the acid with the *least* number of carbon atoms predominated. Although Autenrieth published two further papers, reiterating his original claims (6, 7), there is no doubt that Béhal's results conform better with later work and with modern theoretical expectation.

Kahn was apparently the first worker to consider the effect of relative acid strength on the reactions of mixed anhydrides (138). Three aromatic mixed anhydrides were prepared: benzoic *p*-nitrobenzoic anhydride, which on treat-

ment with alcohol gave exclusively ethyl *p*-nitrobenzoate and benzoic acid; benzoic cumic anhydride, which gave a mixture of esters (ethyl cumate, 20 per cent); and benzoic mesitoic (2,4,6-trimethylbenzoic) anhydride, which gave exclusively ethyl mesitoate. Thus benzoic *p*-nitrobenzoic anhydride yields exclusively the ester of the stronger acid; benzoic cumic anhydride, where the acids are of approximately the same strength, yields a mixture; but benzoic mesitoic anhydride yields exclusively the ester of the weaker acid.

The effect of the relative strength of the component acids in mixed anhydrides was further investigated by Baroni (19), who prepared mixed anhydrides from acetic acid and chloro-substituted acetic and butyric acids. Although mixed anhydrides of this type had been previously reported (3, 102, 205), no attempt had been made to study their chemical properties. Baroni found that in both esterification and aminolysis these mixed anhydrides yielded principally the acyl derivative of the stronger acid. Later work has, on the whole, confirmed these conclusions (80, 128, 173, 211). However, it is quite evident that in certain circumstances mixed anhydrides react to give the ester or amide derived from the weaker acid. Examples of this abnormal reaction include the esterification of benzoic mesitoic anhydride already cited, the aminolysis of benzoic acetic anhydride (25, 127, 212), and the aminolysis of acetic trichloroacetic anhydride (81). Formic acetic anhydride normally reacts with alcohols to give the formate ester (23, 126), but when this reaction is catalyzed by sulfuric acid, the acetate ester is prepared (126). When mixed anhydrides take part in Friedel-Crafts acylation in the presence of aluminum chloride, the ketone derived from the weaker acid appears to predominate (213, 214). The most important observation of all, however, comes from the work of Emery and Gold, which shows that in the reaction of acetic chloroacetic anhydride with aromatic amines the course of the reaction may be profoundly altered by the solvent in which the reaction occurs (80).

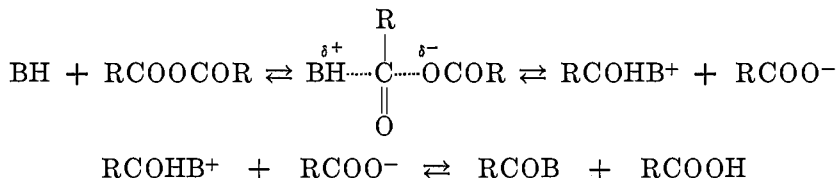
Some insight into the apparently conflicting reactions of mixed anhydrides can be obtained by considering the principal factors involved. The most important factor in all these reactions is the equilibrium between the unsymmetrical anhydride and the two symmetrical anhydrides. The position of the equilibrium



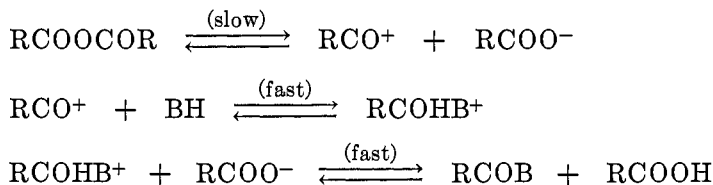
appears to vary very considerably. Thus with similar acids, such as acetic and butyric, the equilibrium composition is that predicted by simple statistical requirements, i.e., with the equilibrium constant equal to 4 (45). On the other hand, in mixed anhydrides of trifluoroacetic acid and other carboxylic acids the equilibrium apparently favors the formation of the unsymmetrical anhydride (42, 89), while acetic benzoic anhydride, prepared from ketene and benzoic acid, is largely disproportionated on standing for 24 hr., showing that the equilibrium favors the two symmetrical anhydrides (127). In general the rate of establishment of the equilibrium appears to be fairly slow, but capable of acceleration by both acidic and basic catalysts. Reactions such as esterification and aminolysis of carboxylic anhydrides are relatively fast, and when a mixed

anhydride which is known to be rich in the unsymmetrical anhydride is treated with an alcohol or amine, the concurrent disproportionation is in most cases too slow to have an appreciable effect on the main reaction.

The uncatalyzed reactions of carboxylic anhydrides can be divided into two categories. Firstly, those involving a bimolecular displacement of the  $S_N2$  type, classically represented thus (74):<sup>2</sup>



Secondly, those in which the anhydride undergoes preliminary ionization and which can be compared to an  $S_N1$  reaction:



The distinction between these two mechanisms should not be regarded as rigid (see page 816), but for the purposes of discussion the division is useful. There can be little doubt that the bimolecular mechanism is the one normally encountered. It is evident that this mechanism, when applied to an unsymmetrical anhydride, favors the formation of the acyl derivative of the stronger acid, since nucleophilic attack will occur preferentially at the carbonyl group most deficient of electrons. Turning to the  $S_N1$  mechanism, it may be expected that heterolytic fission will be more likely with an unsymmetrical molecule, and further that ionization will give the normal negative ion of the stronger acid together with the acylium ion of the weaker acid, rather than the reverse, so that the overall reaction will result in the acyl derivative of the weaker acid being prepared.

Returning to the reported reactions of mixed anhydride solutions, the predominant preparation of the acyl derivative derived from the stronger acid is consistent with the  $S_N2$  mechanism. It is not so certain that the anomalous examples in which the acyl derivative of the weaker acid is formed can all be explained by the occurrence of an  $S_N1$  mechanism in these particular cases. The most striking example of the anomalous reaction is that of trichloroacetic acetic mixed anhydride with 2,4-dichloroaniline to yield almost exclusively 2,4-dichloroacetanilide (81). Emery and Gold discuss their results at some length and conclude that a bimolecular mechanism is operative. In comparing the reactions of acetic chloroacetic anhydride, acetic dichloroacetic anhydride, and acetic trichloroacetic anhydride, steric influences are assumed to have a greatly

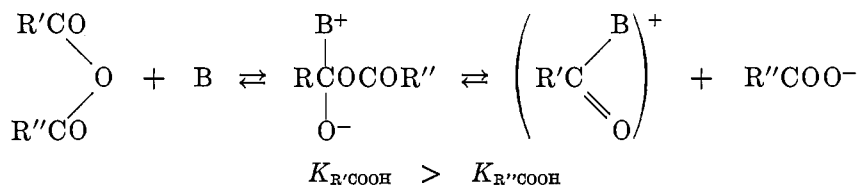
<sup>2</sup> Recent work indicates that this is probably a poor representation of the transition state (*cf.* 26).

increasing effect, so that the combined influence of the electronic and steric effects in opposition to each other explains the chloroacetylation ratios (chloroacetanilide/acetanilide) obtained from the three mixed anhydrides with 2,4-dichloroacetaniline in benzene solution.

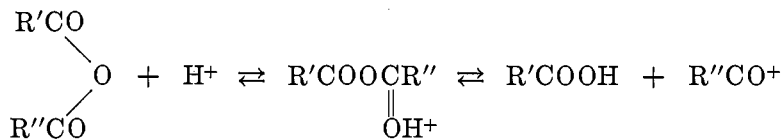
|                              |     |     |   |      |
|------------------------------|-----|-----|---|------|
| Anhydride.....               |     |     |   |      |
| Chloroacetylation ratio..... | 6.1 | 2.3 | 1 | 0.08 |

Similar arguments can be applied to most of the other anomalous reactions. However, the reaction of benzoic mesitoic mixed anhydride to yield the ester of the weaker acid cannot be explained in terms of steric hindrance, since the far more sterically hindered acyl derivative is prepared. In this case the 2,4,6-trimethylbenzoylium ion is known to be particularly stable (110), and thus the ionization is likely to be especially favored. This reaction, therefore, probably provides an example of the unimolecular mechanism.

The effect of catalysts on the reactions of mixed anhydrides is complex, for not only may they influence the course of the reaction, but they can complicate the problem by accelerating the disproportionation of the unsymmetrical anhydride. Neglecting this latter effect, a tertiary base has been represented as favoring acylation by the stronger acyl group (*cf.* 107a),



whereas an acid catalyst promotes the ionization encountered in the uncatalyzed  $\text{S}_{\text{N}}1$  mechanism, resulting in acylation by the weaker acyl group.



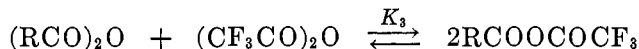
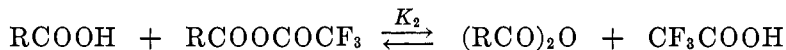
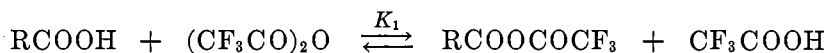
This effect of an acid catalyst may explain the change of acylation from formylation when formic acetic anhydride reacts with alcohols in the presence of sulfuric acid (*cf.* page 807), and acid catalysis is probably also important in trifluoroacetic anhydride systems (see below).

It would be out of place to discuss the reactions of mixed anhydrides in greater detail, but it must be emphasized that the above treatment is not adequate to explain all the reported reactions. Important factors such as the solvent have

been completely neglected, and the division into  $S_N1$  and  $S_N2$  mechanisms provides a deliberately oversimplified view.

2. *Mixed anhydride systems containing trifluoroacetic anhydride*

When a carboxylic acid is dissolved in trifluoroacetic anhydride the following equilibria are established:



These equilibria are related, so that if  $K_1$ ,  $K_2$ , and  $K_3$  are the equilibrium constants, then  $K_1/K_2 = K_3$ . Although no precise values for these constants are known, some idea of their relative magnitude can be obtained.

Morgan determined the van't Hoff depression constant for dilute solutions of trifluoroacetic anhydride in acetic acid and obtained a value of approximately 2 (158). This could be consistent with a variety of compositions, but it does exclude the extreme cases of no reaction ( $i = 1$ ) and of complete conversion of the trifluoroacetic anhydride to acetic anhydride and trifluoroacetic acid ( $i = 3$ )



Observations of the infrared spectra of acetic/trifluoroacetic anhydride mixtures, using a method similar to that of Brown and Trotter (45), have enabled an estimation of the proportion of the unsymmetrical anhydride to be made (41, 42). According to these results the equilibrium is very much in favor of the unsymmetrical molecule. Similar studies of trifluoroacetic/carboxylic mixed anhydrides and of solutions of carboxylic acids in trifluoroacetic anhydride all appear to indicate that the unsymmetrical anhydride is present in almost the maximum proportion stoichiometrically possible (42, 89). So completely is the unsymmetrical anhydride believed to be favored that trifluoroacetic/carboxylic mixed anhydrides have been regarded as consisting solely of the unsymmetrical anhydride (42, 85, 89). These mixed anhydrides have been prepared: (1) from silver trifluoroacetate and an acid chloride (89); (2) by treating a carboxylic acid with an excess of trifluoroacetic anhydride, removing the trifluoroacetic acid formed *in vacuo*, and then flash-distilling the mixed anhydride (85); (3) by treating an ether solution of a carboxylic acid and trifluoroacetic anhydride with a tertiary base, separating by filtration the crystalline trifluoroacetate formed, and recovering the mixed anhydride by distillation (42); (4) by warming a mixture of the two symmetrical anhydrides and then distilling (42). The materials so obtained have definite boiling points and analyze accurately for the mixed anhydride.

These results would seem to establish that in trifluoroacetic mixed anhydride



systems the unsymmetrical anhydride is greatly favored. However, the direct evidence is chiefly based on infrared spectra. The fact that trifluoroacetic acid forms stable addition compounds with ethers, aldehydes, and esters (112, 152) (*cf.* Van der Haar's work mentioned above, page 806) makes it desirable that final proof of the composition of these mixed anhydrides should be obtained, either from kinetic work or from molecular weight determinations. In the opinion of the reviewer it is most probable that such work will confirm the presence of the unsymmetrical anhydride; therefore for the rest of this discussion this will be assumed.

The reactions of these mixed anhydrides are not the same as those of the solutions of carboxylic acids in trifluoroacetic anhydride used in the syntheses. When treated with alcohols they give a mixture of esters derived from both acids, and although when treated with anisole they give exclusively the ketone derived from the hydrocarbon acid, the rate of reaction is much less than when an equimolecular solution of the hydrocarbon acid in trifluoroacetic anhydride is used. However, the addition of 1 mole of trifluoroacetic acid to these mixed anhydrides makes the total stoichiometric composition the same as that of the anhydride solution used for synthesis and at the same time restores the reactivity of the system (42).

Since all the equilibria are reversible, the addition of trifluoroacetic acid to a carboxylic acid anhydride should result in the formation of some unsymmetrical anhydride (37). The reactions of such systems are very similar to solutions of carboxylic acids in trifluoroacetic anhydride, and they are effective for the preparation of esters (159, 160) and of aromatic ketones (167).

Returning to the species present in solutions of carboxylic acid in trifluoroacetic anhydride it is clear that five molecular types could be present: RCOOH; (RCO)<sub>2</sub>O; (CF<sub>3</sub>CO)<sub>2</sub>O; CF<sub>3</sub>COOH; RCOOCOCF<sub>3</sub>; according to the above discussion, two greatly predominate, CF<sub>3</sub>COOH and RCOOCOCF<sub>3</sub>. Besides these molecular species, conductivity measurements indicate the presence of small concentrations of ions. A complete study of the conductivity of the ternary system (CH<sub>3</sub>CO)<sub>2</sub>O-H<sub>2</sub>O-(CF<sub>3</sub>CO)<sub>2</sub>O has been made (175), and from these results it has been concluded that the principal ions in acetic/trifluoroacetic, acid/anhydride mixtures are CH<sub>3</sub>COOH<sub>2</sub><sup>+</sup> and CF<sub>3</sub>COO<sup>-</sup>, together with some additional positive ion which could be (CH<sub>3</sub>CO)<sub>2</sub>OH<sup>+</sup> or CH<sub>3</sub>CO<sup>+</sup>. The fact that there is a rise in conductivity when trifluoroacetic anhydride, which has a very low specific conductivity indeed, is added to acetic anhydride has been interpreted as evidence for the ionization of the unsymmetrical anhydride (175).



The extent of this ionization is very small; its extent in solutions of other acids in trifluoroacetic anhydride will clearly depend on the relative strength of the solute acid. Trifluoroacetic acid has frequently been referred to as a strong acid; this is not so. It has a measurable dissociation constant [ $K_a = 0.58$  (117)] and comparison of its strength with that of the mineral acids can be obtained by comparing their conductivities in acetic acid (175). Recent work on its acidity

in aqueous systems shows even more convincingly how considerably it differs from the mineral acids (176).

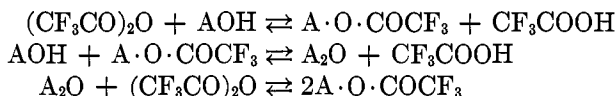
Before attempting to discuss a general mechanism of the condensing reactions of trifluoroacetic anhydride, it will be of value to summarize the cogent facts arising out of the synthetic reactions described in previous sections. This is best achieved by enumeration: (1) Acylation by trifluoroacetic anhydride solutions requires one molecule of the anhydride, and one molecule of the solute carboxylic acid, for each molecule to be acylated. (2) The stronger the solute acid, the less effective the acylating properties of the solution. (3) The acylating entity of these solutions is a far more reactive species than a normal carboxylic anhydride molecule. (4) Acylation is inhibited by basic substances, and this may be due to specific inhibition by the trifluoroacetate ion.

These then are the experimental facts and it is the purpose of the next subsection to attempt to relate all these observations to a simple mechanism.

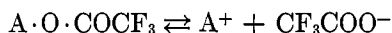
#### B. A MECHANISM FOR THE ACYLATION REACTIONS PERFORMED BY SOLUTIONS OF OXY ACIDS IN TRIFLUOROACETIC ANHYDRIDE

##### 1. Ionization of the unsymmetrical anhydride

When a weak oxy acid (A·OH) is dissolved in trifluoroacetic anhydride, a series of interrelated equilibria are established (*cf.* page 810).



It has been proposed that in addition to these three interrelated equilibria, there is partial ionization of the molecule of the unsymmetrical anhydride [ $\text{A}\cdot\text{O}\cdot\text{COCF}_3$ ] (36, 37).



It has further been postulated that although the degree of ionization is extremely small, it is the great reactivity of these ions which is principally responsible for the acylating properties of the trifluoroacetic anhydride solutions (36, 37).

Table 4 includes all the acids which have been used in trifluoroacetic anhydride solutions, together with the acyl ions derived from them and the reactions

TABLE 4  
*Cations derived from the solute oxy acids*

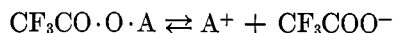
| Oxy Acid A·OH                                     | Ion A <sup>+</sup>   | Reactions† | Oxy Acid A·OH                    | Ion A <sup>+</sup>               | Reactions† |
|---|--|------------|----------------------------------|----------------------------------|------------|
| RCOOH   | RCO <sup>+</sup>   | I, II, III | NO <sub>2</sub> OH               | NO <sub>2</sub> <sup>+</sup>     | I, II      |
| (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> COH | (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C <sup>+</sup> | —          | ROPO <sub>2</sub> H <sub>2</sub> | ROPO <sub>2</sub> H <sup>+</sup> | I          |
| ArSO <sub>2</sub> OH                              | ArSO <sub>2</sub> <sup>+</sup>                               | I, II      | BrOH*                            | Br <sup>+</sup>                  | II         |
| NOOH  | NO <sup>+</sup>  | II, III    | IOH*                             | I <sup>+</sup>                   | II         |

\* Hypothetical oxy acids never isolated.

† I = esterification (Section I); II = electrophilic substitution of aromatic compounds (Section II); III = acyl-addition to unsaturated compounds (Section III).

that have been reported. This table is not intended to imply that all these acids are in fact ionized in this fashion by trifluoroacetic anhydride; the reactions of each acid will be considered separately later.

In terms of the above discussion on mixed anhydrides the second postulate implies that the  $S_N1$  reaction predominates in trifluoroacetic anhydride solutions. However, it does not follow that the bimolecular mechanism can be disregarded. The predominance of the  $S_N1$  mechanism can be attributed to two factors: (1) the extreme reactivity of the ion  $A^+$ , and (2) the fact that the ionization step



although rate determining, is fast when compared with the bimolecular reaction. This state of affairs is likely to occur in syntheses of ketones and in the esterification of unreactive hydroxy compounds. But with highly reactive primary alcohols the rate-determining step of the bimolecular reaction is comparatively accelerated, whereas that of the ionization reaction is unaffected, so that bimolecular esterification does compete to some extent. This of course implies a change from acylation exclusively by the ion  $A^+$ , giving derivatives of  $A \cdot OH$  only, to a competitive acylation by  $A^+$  and  $CF_3CO \cdot O \cdot A$ , giving a mixture of derivatives of both trifluoroacetic acid and  $A \cdot OH$ . There is experimental evidence of this phenomenon (see Section I).

The combination of the equilibria and ionization proposed can also account for the acylating properties of mixtures of trifluoroacetic acid and a carboxylic acid anhydride, and explains the effectiveness of trifluoroacetic acid in less than stoichiometric amounts in such systems (37).

The effect of basic substances on esterification and the synthesis of ketones has been attributed to a suppression of the ionization of the unsymmetrical anhydride by trifluoroacetate ions formed through interaction of the base with the free trifluoroacetic acid present (34, 37). The addition of sodium trifluoroacetate should retard the reactions in a similar manner, through the common-ion effect. Evidence of the phenomenon has been obtained (36), although the effect is not so marked as might be expected if this were the only effect that bases have on the system. The reaction of trifluoroacetic anhydride solutions with amines to yield a mixture of amides has been attributed to a similar suppression of ionization, coupled with a very rapid bimolecular reaction. It must be added that the steric effects that Emery and Gold postulate for the reaction of acetic trichloroacetic mixed anhydride (81) are not likely to be important with trifluoroacetic acid derivatives, because of the relative sizes of the chlorine and fluorine atoms.

So far it has been assumed that the formation of the acyl ion  $A^+$  occurs entirely by the spontaneous ionization of the unsymmetrical anhydride, i.e., by the uncatalyzed  $S_N1$  mechanism. However, there are reasons for believing that this ionization is in fact facilitated by acidic catalysis (*cf.* page 809). The importance of the acidity of these systems is emphasized by the difference between the reactions of trifluoroacetic mixed anhydrides and those of solutions of carboxylic acids in trifluoroacetic anhydride. The stoichiometric difference between the

mixed anhydrides and the systems used for synthetic reactions is simply 1 mole of trifluoroacetic acid (*cf.* page 811). The additional trifluoroacetic acid is unlikely to increase the dielectric constant greatly and hence the ionizing properties of the solution (198); therefore the difference in the acylating properties of the two solutions must be attributed to the difference in their acidity. This suggests that the acyl ion  $A^+$  is principally formed through the acid-catalyzed ionization of the unsymmetrical anhydride  $CF_3CO \cdot O \cdot A$  rather than by its slow spontaneous dissociation.



If this view is correct, then it is necessary to modify the original mechanism (36, 37) and instead of attributing the reactivity of trifluoroacetic anhydride solutions solely to the spontaneous ionizations of the unsymmetrical anhydride (page 812), it may in some cases be more correctly attributed to the acid-catalyzed ionization of this molecule. In the ordinary synthetic reactions the trifluoroacetic acid formed acts as the catalyst. On this view, basic substances not only suppress spontaneous ionization through the common-ion effect, but also inhibit the more important acid-catalyzed ionization. In some cases the base may also accelerate the bimolecular reaction (*cf.* page 809), but usually the inhibition of the acid-catalyzed ionization is sufficient to explain the change in the course of the reaction.

In conclusion, it may be said that the acylating properties of solutions of weak oxy acids in trifluoroacetic anhydride are attributed to acyl ions  $A^+$  derived from the ionization of the unsymmetrical anhydride  $CF_3CO \cdot O \cdot A$ . In some cases (notably when  $A$  is Br or I) this ionization is probably spontaneous, but usually it is accelerated by general acid catalysis, the trifluoroacetic acid present in these systems being important in this respect. Finally, although for clarity the mechanism has been represented as a discrete ionization followed by electrophilic attack by the ion formed, the whole process of ionization and substitution may take place during a single collision. If this is so, then the division into  $S_N1$  and  $S_N2$  becomes artificial; both processes are bimolecular and differ only in the electronic structures of their transition states.

## 2. *An interpretation of the synthetic reactions*

In the previous subsection a mechanism was described which attributed the principal synthetic reactions of trifluoroacetic anhydride to reactive acyl ions present in these systems. It remains to discuss the actual manner in which the various synthetic reactions occur.

Acylium ions ( $RCO^+$ ) have long been recognized as possible intermediates in acid-catalyzed esterification (73, 74). However, it has only been definitely established that esterification proceeds through acylium ions for certain specific sterically hindered acids, when reacting in sulfuric acid solution (110, 148, 165, 168). The existence of acylium ions derived from simple carboxylic acids like acetic and benzoic acids has been well established (182, 183, 184) and strong evidence has been provided to show that these ions are intermediates in other

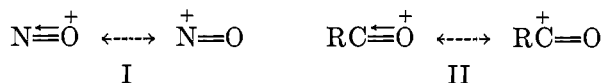
reactions (48, 49, 50, 155). Thus no new principle is required to extend the concept of esterification by acylium ions from the known examples of sterically hindered acids in sulfuric acid to the general esterification of carboxylic acids in trifluoroacetic anhydride. Esterifications performed in this medium show all the characteristics that would be expected if acylium ions were reaction intermediates. The overall reaction rate is rapid and it shows little sensitivity to steric effects. The effectiveness of the reaction is decreased by an increase in the strength of the solute acid, because although the acylium ion so formed will be more reactive, the rate-determining ionization step is retarded, allowing the bimolecular reaction with its consequent trifluoroacetylation to compete.

Previous evidence for the occurrence of acyl ions in esterifications of acids other than carboxylic acids is limited to nitric acid and the nitronium ion (31, 136), and it is possible that some of the trifluoroacetic anhydride reactions may go through molecular mechanisms. Thus the preparation of cyclic phosphates (*cf.* page 792) may well proceed by a bimolecular reaction of the unsymmetrical anhydride, and the synthesis of nitrate esters may actually be performed by the symmetrical anhydride ( $N_2O_5$ ) present in the system (this will be discussed again in connection with aromatic nitration). On the other hand, the preparation of esters of *p*-toluenesulfonic acid probably does go through the sulfonylium ion ( $RSO_2^+$ ), in spite of the acidic strength of *p*-toluenesulfonic acid. Possibly the sulfonylium ions are stabilized by the large number of possible canonical forms.

Acylium ions have for a long time been regarded as intermediates in Friedel-Crafts acylation (87) and though the universality of such a mechanism is now in doubt (197), it remains fairly certain that these ions are intermediates in certain circumstances. In particular there are strong reasons for believing that acetylation by acid-catalyzed acetic anhydride and by acetyl perchlorate proceeds through acylium ions (48, 49, 155). The syntheses of aromatic ketones performed in trifluoroacetic anhydride are all consistent with the ionic mechanism, and the failure of these systems to acylate unactivated aromatic nuclei has been attributed to the relatively low reactivity of these ions (197). Evidence is also available that the synthesis of sulfones can proceed through sulfonylium ions (47) and here too the reactions in trifluoroacetic anhydride are consistent with an ionic mechanism.

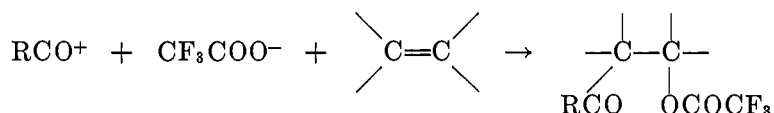
Nitration by the nitronium ion ( $NO_2^+$ ) is now well established (125), and it would seem reasonable to postulate these ions as the reactive entities in trifluoroacetic anhydride systems. However, since nitric acid is considerably stronger than trifluoroacetic acid, it may well be that nitrations performed by solutions of nitric acid in trifluoroacetic anhydride are largely effected by dinitrogen pentoxide (107), though the preparation of 2,4-dinitrobromobenzene suggests reaction by the nitronium ion. It has already been pointed out that the formation of diazonium salts in solutions of nitrous acid and trifluoroacetic anhydride probably proceeds through preliminary nitrosylation. Nitrosylation by the nitrosonium ion ( $NO^+$ ) is generally accepted (46), and the similarity in the scope of this reaction to the synthesis of ketones has been attributed to the

similar electronic structure and hence reactivity of the nitrosonium (I) and acylium (II) ions (197).



Numerous instances of the ionic halogenation of aromatic nuclei have been established (135), and strong evidence has been provided to show that halogenation by trifluoroacetyl hypohalites proceeds by an ionic mechanism (111, 124).

The synthesis of keto olefins and  $\beta$ -diketones has been described in terms of an ionic addition across the unsaturated linkage.



The direction of addition in all the reactions that have been reported is consistent with an initial electrophilic attack by the acylium ion.

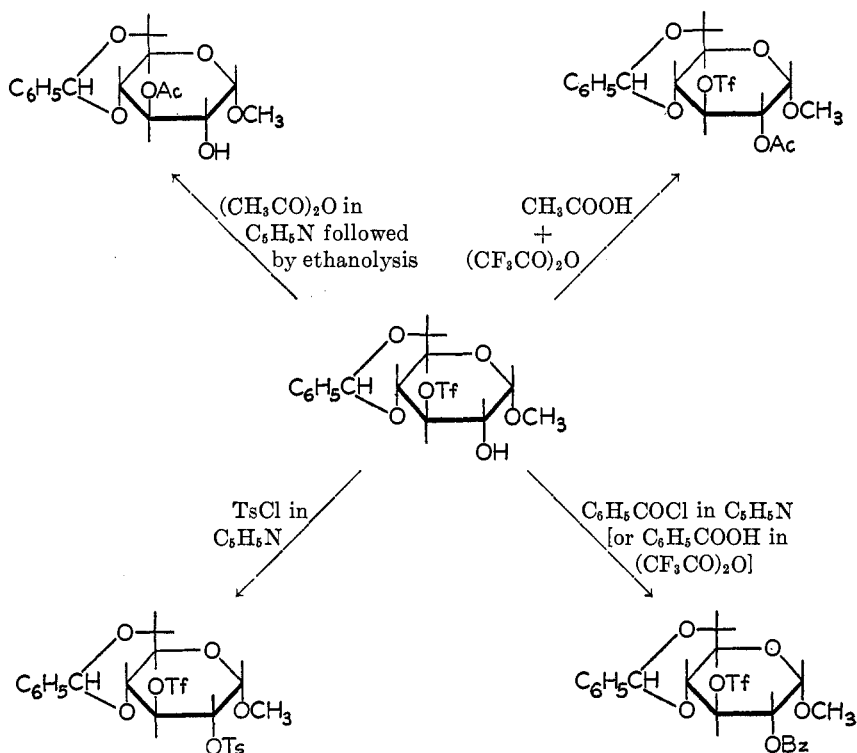
In conclusion, it will be seen that the simple ionic mechanism is capable of explaining all the reported reactions of trifluoroacetic anhydride solutions in terms of reaction mechanisms already established or generally accepted and without recourse to any *ad hoc* assumptions. Of recent years there has been some doubt as to the reality of the  $\text{S}_{\text{N}}1$  mechanism. It is possible to explain some of the reactions of trifluoroacetic anhydride along very similar lines to those already discussed, but in terms of a changing bimolecular mechanism. In such a mechanism it is assumed that in some reactions bond making is all important (this corresponds almost exactly to the  $\text{S}_{\text{N}}2$  mechanism already discussed (page 808)), while in other reactions bond breaking is more important (the  $\text{S}_{\text{N}}1$  mechanism (page 808) forms the extreme case of this mechanism, in which bond breaking has commenced before bond making has begun). This argument has drawbacks, and even if it were found to approach nearer to physical reality than the present ionic mechanism, it is unlikely to prove so profitable for prediction.

## VII. OTHER USES OF TRIFLUOROACETIC ACID DERIVATIVES

### A. TRIFLUOROACETYL RESIDUES AS BLOCKING GROUPS

The ease with which trifluoroacetyl groups can be hydrolyzed has led to their use as blocking agents in syntheses of carbohydrates, steroids, and polypeptides. The readiness with which trifluoroacetyl derivatives undergo hydrolysis was first reported by Swarts in his original work on trifluoroacetic acid (192). No attempt was made to utilize this property, until trifluoroacetate esters of carbohydrates were synthesized by the Birmingham school. These compounds, and polyhydroxy alcohol trifluoroacetates in general, hydrolyze so readily that it is impossible to isolate them from aqueous mixtures. The compounds, which are prepared by treating the hydroxy compound with trifluoroacetic anhydride, can

be isolated by adding dry carbon tetrachloride to the reaction mixture and distilling *in vacuo* to remove the trifluoroacetic acid formed, together with any excess anhydride (43). Although trifluoroacetic acid is a relatively strong acid, carbohydrate trifluoroacetates are hydrolyzed without Walden inversion or anhydro-ring formation (43). Trifluoroacetyl groups are most conveniently removed by methanolysis, a method which is equally applicable to labile polyhydroxy alcohol derivatives (38) or to simple esters (86, 121). In some cases it has been found possible to remove the trifluoroacetyl groups from carbohydrates severally. The compound most studied is methyl 4,6-*O*-benzylidene-2,3-bis-*O*-trifluoroacetyl- $\alpha$ -D-glucopyranoside, which readily undergoes partial methanolysis to yield a monotrifluoroacetate, fairly definitely established as the 3-*O*-trifluoroacetyl derivative (35, 38). The reactions of this compound are summarized below:



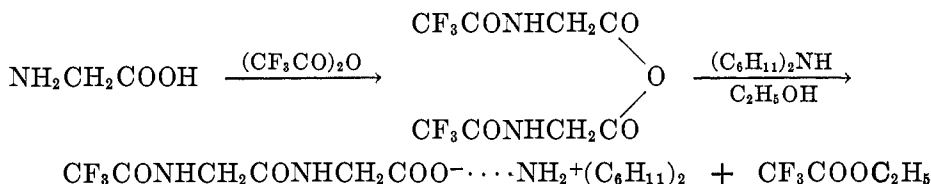
Ac =  $\text{CH}_3\text{CO}$ , Tf =  $\text{CF}_3\text{CO}$ , Ts =  $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_2$ , Bz =  $\text{C}_6\text{H}_5\text{CO}$ .

It will be noticed that the trifluoroacetyl group is unaffected by benzylation and tosylation in pyridine, or by benzylation and acetylation in trifluoroacetic anhydride. But acetylation by acetic anhydride in pyridine results in apparent migration from the 3-position to the 2-position, so that the acetyl group enters at the 3-hydroxy group. This effect must presumably be attributed to the more basic nature of this medium, compared with benzoyl (or tosyl) chloride in

pyridine. A similar migration of a trifluoroacetyl group is believed to occur with *l*-rhamnose (51).

Trifluoroacetyl groups have recently been utilized as blocking agents in the synthesis of steroids (150, 151). In both investigations trifluoroacetyl groups were used for protecting hydroxyl groups during Arndt-Eistert syntheses which involved preparing trifluoroacetates of free steroid acids. In model experiments with the carboxyl group blocked, crystalline trifluoroacetate derivatives were isolated, but in the main experiments, which require the preparation of trifluoroacetate derivatives of hydroxy acids, the products were amorphous. Probably some polyester formation occurred, and as a result the final overall yields of the synthesis were low. In one model experiment preferential hydrolysis of the 3-*O*-trifluoroacetyl group in 3 $\beta$ ,11 $\beta$ -(bis-*O*-trifluoroacetyl)alloetic acid methyl ester was obtained by treatment with potassium bicarbonate (2 hr. at 20°C.); the 11 $\beta$ -*O*-trifluoroacetyl group was hydrolyzed by methanolic potassium carbonate (24 hr. at 20°C.) (151).

Some properties of *N*-trifluoroacetyl amino acids have been discussed in Section IV. The importance of these compounds as blocking agents lies in the ease with which they can be hydrolyzed. They are completely hydrolyzed by *N*/5 sodium hydroxide in 10 min., under which conditions amino acid amides and dipeptides are unaffected (206). The value of such a blocking group in the synthesis of peptides is obvious, and it was first used by Weygand and Leising who, besides developing the dipeptide synthesis in Section IV, used *N*-trifluoroacetyl amino acid anhydrides (prepared using trifluoroacetic anhydride and a tertiary base) and *N*-trifluoroacetyl amino acid chlorides (prepared conventionally by treating the *N*-trifluoroacetyl amino acid with thionyl chloride) to prepare dipeptides. More recently Weygand and Reiher have used trifluoroacetyl residues as blocking groups in other established peptide syntheses and also two new syntheses employing them (208). The most interesting of these involves the reaction of *N*-trifluoroacetyl glycine anhydride with dicyclohexylamine in ethanol.



*N*-Trifluoroacetyl groups have also been used in the synthesis of *O*-glucosides of phenolic amino acids (195), and the rates of the enzymic hydrolysis of *N*-trifluoroacetyl derivatives of amino acids have been studied (97, 98).

Weygand and his coworkers have prepared *N*-trifluoroacetyl amino acids by treating the free amino acid with a molecular equivalent of trifluoroacetic anhydride. Although some racemization takes place in excess anhydride (206), a large number of optically active amino acids have been trifluoroacetylated by this method without racemization (98). However, the use of ethylthiol trifluoro-



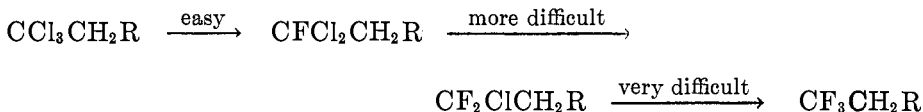


such ionization is unlikely and the reactions are probably bimolecular (possibly even homolytic). However, it has been suggested that the hydroxyl cation  $\text{OH}^+$  does occur in the transition state and it is possible that the tendency of the peroxytrifluoroacetic acid molecule to undergo heterolytic fission accounts for the reactivity of these systems (82).

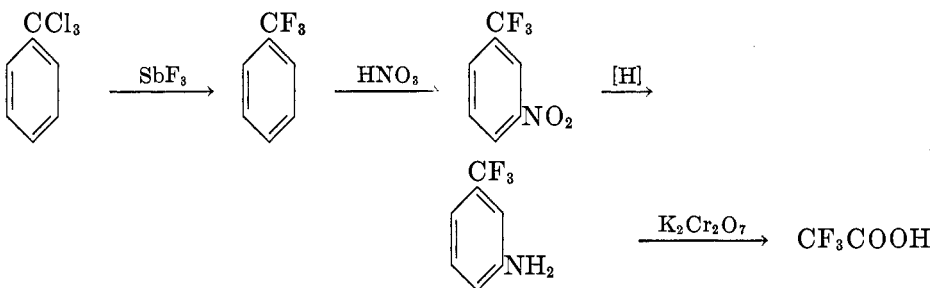
## VIII. THE PREPARATION OF TRIFLUOROACETIC ACID AND ANHYDRIDE

### A. PREPARATION OF TRIFLUOROACETIC ACID

Trifluoroacetic acid was first prepared by Swarts in 1922. In his extensive studies of fluorine compounds, Swarts had prepared many aliphatic fluorine derivatives by replacement of chlorine atoms using antimony trifluoride together with catalytic amounts of pentavalent antimony (the "Swarts reaction"). However, he was unable to exchange more than two atoms by fluorine in a  $\text{CCl}_3$ - group attached to an aliphatic chain.



This has since been achieved by Henne (118, 122) and by other workers, but it remains a difficult reaction. Swarts, however, found that benzotrichloride behaved differently and could readily be converted into benzotrifluoride by using antimony trifluoride. It was by the oxidation of trifluoromethylcyclohexane, prepared by the hydrogenation of benzotrifluoride, that Swarts first obtained trifluoroacetic acid (192). Having discovered that the  $\text{CF}_3$ - group was stable to vigorous oxidation, he at once developed a practical method for the preparation of trifluoroacetic acid (193).



Benzotrifluoride is now a readily obtainable chemical, and some subsequent steps in Swarts's synthesis of trifluoroacetic acid have been improved (113). This remains the most satisfactory method for its laboratory preparation.

The first synthesis of trifluoroacetic acid capable of development for commercial use was developed by Henne and his coworkers. They found that a  $\text{CCl}_3$ - group adjacent to a double bond was like that in benzotrichloride and could be completely fluorinated under relatively mild conditions (123). Oxida-

TABLE 5  
*Physical properties of trifluoroacetic anhydride and trifluoroacetic acid*

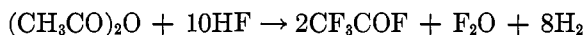
| Physical Property                      | (CF <sub>3</sub> CO) <sub>2</sub> O | CF <sub>3</sub> COOH              |
|--|-------------------------------------|-----------------------------------|
| Freezing point, °C.....                | -65                                 | -15.5                             |
| Boiling point, °C.....                 | 39                                  | 71.5*                             |
| Density, grams/cc.....                 | 1.4951/25°C.                        | 1.4890/20°C.                      |
| Viscosity, poises.....                 | —                                   | 0.00876/20°C.                     |
| Refractive index, n <sub>D</sub> ..... | 1.2680/25°C.                        | 1.2850/20°C.                      |
| Specific conductivity, mhos.....       | 1 × 10 <sup>-10</sup> /25°C.        | 3.5-4.2 × 10 <sup>-7</sup> /25°C. |
| Dielectric constant.....               | 2.7/25°C.                           | 8.2/25°C.                         |

\* Trifluoroacetic acid forms with water a constant-boiling mixture boiling at 105.5°C. and containing 79.4 per cent of trifluoroacetic acid.

tion of the double bond in this type of compound led directly to trifluoroacetic acid (116).



A number of patents were taken out for this method (71, 115, 134, 154) and it was developed on a semi-technical scale in both the United States and Great Britain. Although the potential efficiency of the process was improved by the use of perchlorobutadiene as starting material (9, 121), it has been completely superseded by the development of the Simons electrochemical method (185, 186). The exact details of the method by which perfluorocarboxylic acids are prepared have never been fully disclosed, but the procedure has been described in outline (140, 185, 187, 188, 189).



At present this is the only commercial method of preparation in operation, and trifluoroacetic acid can be obtained in semi-industrial quantities in the United States and as a research chemical elsewhere. Many other reactions in which trifluoroacetic acid is produced have been reported (28, 29, 101, 114, 157, 169, 199), but none of these have been developed.

Trifluoroacetic acid is a volatile liquid which fumes in moist air. It has a pungent, but not unpleasant, smell, and it readily attacks the skin. It is best stored in glass vessels, with either a glass stopper or a cap lined with polytetrafluoroethylene. Most common metals, cork, rubber, Bakelite, and polyethylene are all corroded by the acid. The acid and its fumes are toxic because of their acidity, but no other physiological effects have been reported.

#### B. PREPARATION OF TRIFLUOROACETIC ANHYDRIDE

Swarts originally prepared trifluoroacetic anhydride by distilling the acid over phosphoric anhydride (193), and this remains the most convenient method of preparation for use in the laboratory. The anhydride can also be prepared by treating the acid with stabilized sulfur trioxide (77), but this method is not well suited to small-scale laboratory preparation. Because sulfur trioxide boils very close to the boiling point of trifluoroacetic anhydride [SO<sub>3</sub>, b.p. 44.6°C.;

$(\text{CF}_3\text{CO})_2\text{O}$ , b.p. 39–40°C.] it is necessary to use a slight excess of the acid. The use of sulfur trioxide comes into its own for large-scale preparations where the relative costs of phosphoric oxide and sulfur trioxide are important.

Trifluoroacetic anhydride is a volatile liquid which, unlike the acid, does not fume extensively in air. Because the material is so volatile and hygroscopic, it is usually best prepared directly from the acid as and when required. Like trifluoroacetic acid the anhydride can be stored in glass vessels, but it attacks rubber, cork, and most common metals.

The author expresses his thanks to Professor M. Calvin and to Professor F. Weygand for supplying him with details of their work prior to publication. He thanks Professor E. L. Hirst, F.R.S., for his interest and criticism and the University of Edinburgh for the award of an I.C.I. Fellowship. Finally he would like to acknowledge his debt to Professor M. Stacey, F.R.S., and to Drs. E. J. Bourne and J. C. Tatlow of the University of Birmingham, who first interested him in trifluoroacetic anhydride.

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