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NEW METHODS FOR PREPARING *N,N*-DIALKYLTRIFLUOROACETAMIDES

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SUMMARY

N,N-Dialkylacetamides and *N,N*-dialkylformamides can be converted into *N,N*-dialkyltrifluoroacetamides by treatment with either trifluoroacetic anhydride or trifluoroacetic acid.

INTRODUCTION

The initial objective of this work was to prepare partially fluorinated amides as solvents for certain polymeric materials. *N,N*-Dialkyltrifluoroacetamides are conventionally prepared from ethyltrifluoroacetate and the corresponding dialkylamines[1]. Coppinger prepared *N,N*-dimethylacetamide by reacting acetic anhydride with *N,N*-dimethylformamide[2], and a facile method to prepare *N,N*-dimethyltrifluoroacetamide would be to replace acetic anhydride with trifluoroacetic anhydride. This paper describes the synthesis of *N,N*-dialkyltrifluoroacetamides by reacting disubstituted formamides and acetamides with trifluoroacetic anhydride or trifluoroacetic acid. The reactions were studied by gas chromatography and mechanistic interpretations are developed.

RESULTS AND DISCUSSION

Using *N,N*-dimethylacetamide, *N,N*-diethylacetamide and *N,N*-dimethylformamide, reactions (1)–(6) were found to be workable, *N,N*-dialkyltrifluoroacetamides being obtained in good yield (70–90%) except in the case of reaction (4) which resulted in yields less than 10%.

$$(F_3CC)_2O + HC{-}N(CH_3)_2 \rightarrow F_3CC{-}N(CH_3)_2 + F_3CCOH + CO\uparrow \qquad (1)$$

$$(F_3CC)_2O + H_3CC{-}N(CH_3)_2 \rightarrow F_3CC{-}N(CH_3)_2 + H_3CC{-}O{-}CCF_3 \quad (2)$$

$$(F_3CC)_2O + H_3CC{-}N(C_2H_5)_2 \rightarrow F_3CC{-}N(C_2H_5)_2 + H_3CC{-}O{-}CCF_3 \quad (3)$$

$$F_3CCOH + HC{-}N(CH_3)_2 \rightarrow F_3CC{-}N(CH_3)_2 + HCOH \quad (4)$$

$$F_3CCOH + H_3CC{-}N(CH_3)_2 \rightarrow F_3CC{-}N(CH_3)_2 + H_3CCOH \quad (5)$$

$$F_3CCOH + H_3CC{-}N(C_2H_5)_2 \rightarrow F_3CC{-}N(C_2H_5)_2 + H_3CCOH \quad (6)$$

The reaction mechanisms involved in these reactions were next studied.

Figures 1, 2 and 3 are chromatograms for the reactions given by equations (1), (2) and (3), respectively. In those reactions conducted at room temperature a complex was formed, and the chromatograms for the reactions at reflux temperatures indicate various levels of stability for them, apparently related to the basicity of the amides according to the following order:

$$H_3CC{-}N(C_2H_5)_2 > H_3CC{-}N(CH_3)_2 > HC{-}N(CH_3)_2 > F_3CC{-}N(C_2H_5)_2 > F_3CC{-}N(CH_3)_2.$$

During the reaction of trifluoroacetic anhydride with *N,N*-dimethylformamide, formyltrifluoroacetate might have formed. Under these conditions, however, it would be unstable, decomposing into trifluoroacetic acid and carbon monoxide (Fig. 1).

For the reaction of trifluoroacetic anhydride with *N,N*-dimethyl- or *N,N*-diethylacetamide (Figs. 2 and 3), acetyltrifluoroacetate was expected to be formed. However, a peak could not be assigned to it; instead there were peaks with retention times corresponding to those of acetic anhydride, trifluoroacetic acid and/or acetic acid.

The appearance of the peak of acetic anhydride and the absence of the peak of acetyltrifluoroacetate in Figures 2(a), 2(b), 3(a) and 3(b) may be reasonably explained as follows. The acetyltrifluoroacetate formed *in situ* may be assumed to be much more reactive than trifluoroacetic anhydride and as soon as it is produced it reacts immediately with the disubstituted acetamides to form the corresponding trifluoroacetamides and acetic anhydride as postulated in equation (7).

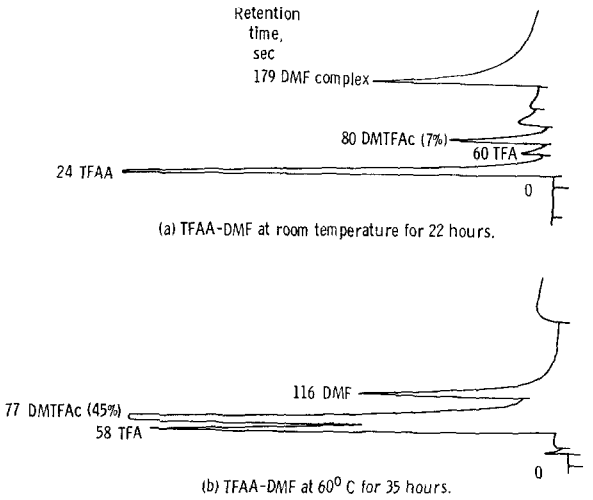


Fig. 1. Gas chromatographic analysis of

$$(F_3CC(=O)-)_2O + HC(=O)-N(CH_3)_2 \longrightarrow F_3CC(=O)-N(CH_3)_2 + F_3CCOH + CO\uparrow.$$

Oven temperature, 110°; helium flow rate, 130 ml min^{-1}; approximate authentic retention times (s): TFAA, 24; TFA, 60; DMTFAc, 78; DMF, 121.

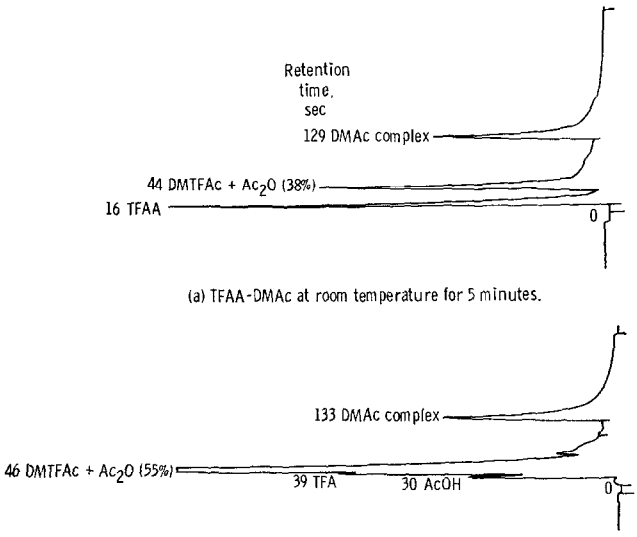
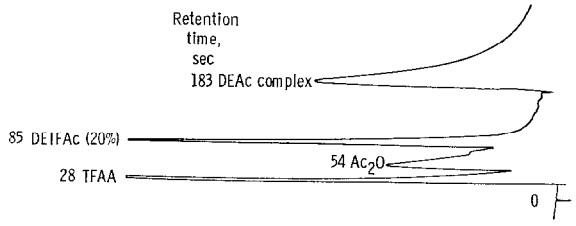


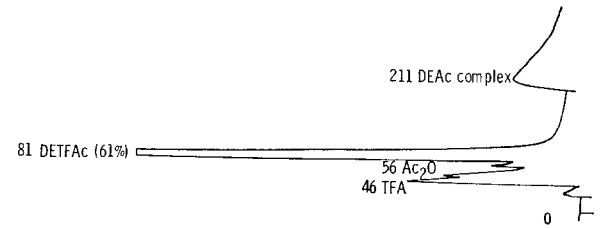
Fig. 2. Gas chromatographic analysis of

$$(F_3CC(=O)-)_2O + H_3CC(=O)-N(CH_3)_2 \longrightarrow F_3CC(=O)-N(CH_3)_2 + H_3CC(=O)-O-C(=O)CF_3.$$

Oven temperature, 120°; helium flow rate, 240 ml min^{-1}; approximate authentic retention times (s): TFAA, 16; ATFA, 23; AcOH, 30; TFA, 37; DMTFAc and Ac_2O, 44; DMAc, 109.

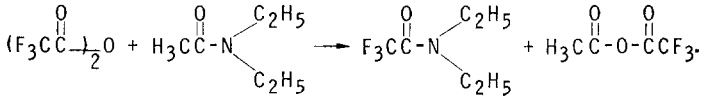


(a) TFAA-DEAc at room temperature for 5 minutes.

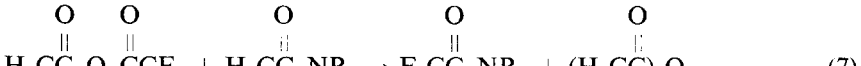


(b) TFAA-DEAc at 140° to 153° C for 17 hours.

Fig. 3. Gas chromatographic analysis of



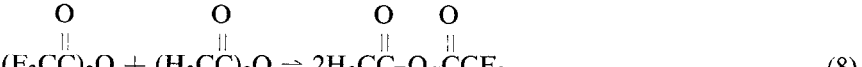
Oven temperature, 150°; helium flow rate, 85 ml min^{-1}; approximate authentic retention times (s): TFAA, 28; ATFA, 36; AcOH, 41; TFA, 46; Ac_2O, 54; DETFAc, 81; DEAc, 160.



(7)

The formation of trifluoroacetic acid and acetic acid during the refluxing of trifluoroacetic anhydride with *N,N*-dimethyl- or *N,N*-diethylacetamide apparently resulted from side-reactions. The drastic reaction conditions could have generated trifluoroacetoxy and acetoxy free radicals which would then abstract hydrogen from the acetamides.

The actual systems were more complicated than just described. The acetic anhydride formed would react with trifluoroacetic anhydride to produce acetyltrifluoroacetate, and the trifluoroacetic acid or acetic acid could also react with acetic anhydride or trifluoroacetic anhydride as shown in the following equilibria equations reported by Bourne *et al.*[3] and Tedder[4]:



(8)

(9)

$$H_3CCOH + (F_3CC)_2O \rightleftharpoons H_3CC{-}O{-}CCF_3 + F_3CCOH \quad (10)$$

The reactions given in equations (8), (9) and (10) were next conducted at room temperature and their course followed by gas chromatography. These results (Figs. 4, 5 and 6) are in good agreement with those of Bourne *et al.*[3] using infrared spectrophotometry, cryoscopy and conductivity measurements. By relative peak area analysis, the percentages of acetyltrifluoroacetate in equilibrium at room temperature were found to be as follows: reaction (8), 90%; reaction (9), 65%; and reaction (10), 25%.

These chromatograms (Figs. 1, 2 and 3) also show that *N,N*-dialkyltrifluoroacetamides were formed at room temperature as well as at reflux temperatures. The rate of reaction of trifluoroacetic anhydride with the disubstituted amides at room temperature was approximately in the following order as given by the relative peak area percentages of *N,N*-dialkyltrifluoroacetamides:

$\text{Rate}_{\text{DEAC}}$ (20%—5 min) $\simeq$ $\text{Rate}_{\text{DMAC}}$ (19%—5 min) $>>$ Rate_{DMF} (7%—22 h).

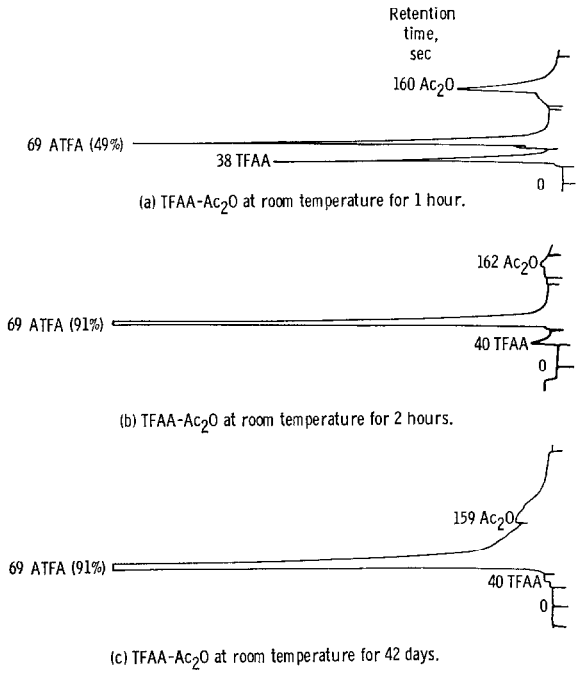


Fig. 4. Gas chromatographic analysis of

$$(F_3C\overset{O}{\overset{\|}{C}}\!\rightarrow\!)_2O + (H_3C\overset{O}{\overset{\|}{C}}\!\rightarrow\!)_2O \rightleftharpoons 2H_3C\overset{O}{\overset{\|}{C}}{-}O{-}\overset{O}{\overset{\|}{C}}CF_3.$$

Oven temperature, 90°; helium flow rate, 70 ml min^{-1}; approximate authentic retention times (s): TFAA, 37; Ac_2O, 159.

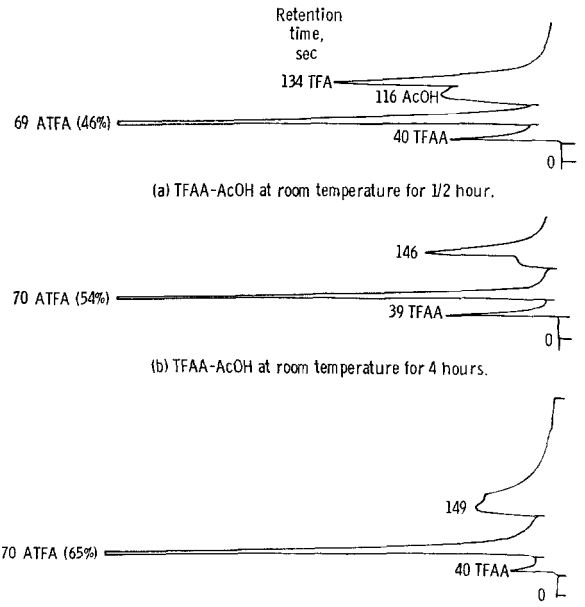


Fig. 5. Gas chromatographic analysis of

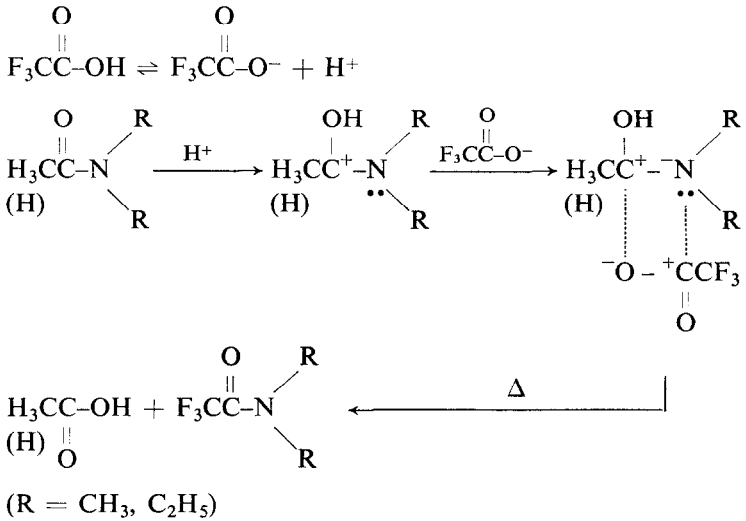
$$(F_3CC\overset{O}{\overset{\|}{}}\!\!\rightarrow_2 O + H_3CC\overset{O}{\overset{\|}{}}OH \rightleftharpoons H_3CC\overset{O}{\overset{\|}{}}\!\!-O-C\overset{O}{\overset{\|}{}}CF_3 + F_3CC\overset{O}{\overset{\|}{}}OH.$$

Oven temperature, 90°; helium flow rate, 70 ml min^{-1}; approximate authentic retention times (s): TFAA, 37; ATFA, 69; AcOH, 99; TFA, 136; Ac_2O, 159.

The chromatograms shown in Figures 7, 8 and 9 indicate that trifluoroacetic acid formed a stable high boiling complex[5] with *N,N*-dimethylacetamide, *N,N*-diethylacetamide, or *N,N*-dimethylformamide, and that heating was necessary for the formation of *N,N*-dialkyltrifluoroacetamides in all three cases. An oxygen-protonated four-center nucleophilic substitution mechanism, similar to the one suggested by Ring *et al.*[6], is proposed for these reactions (see opposite page).

The high boiling complex formed decomposes only upon prolonged heating, and because the carbonyl carbon–nitrogen bond of the trifluoroacetyl group is stronger than that of the acetyl group (or the formyl group) it gives the corresponding dialkyltrifluoroacetamide and acetic (or formic) acid instead of re-forming the initial reactants. It appears that this is an irreversible reaction since no *N,N*-dimethyl- or *N,N*-diethylacetamide was formed when the corresponding dialkyltrifluoroacetamide was refluxed with acetic acid overnight.

For the reactions of trifluoroacetic acid with *N,N*-dimethylacetamide and *N,N*-diethylacetamide at room temperature, the peaks with retention time of 49 s (Fig. 7(a)) and 56 s (Fig. 8(a)) were found to be essentially trifluoroacetic acid.



$(R = CH_3, C_2H_5)$

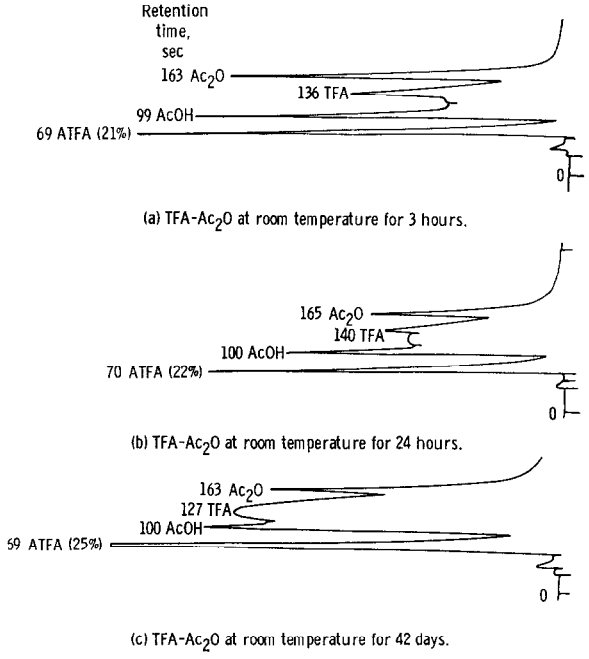
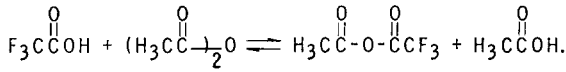
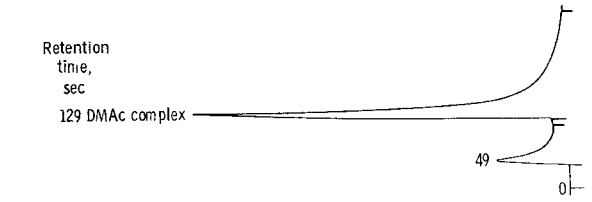


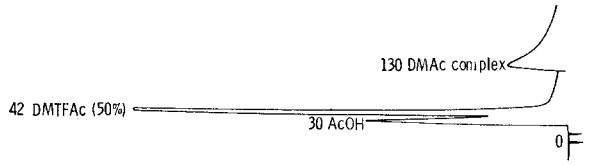
Fig. 6. Gas chromatographic analysis of



Oven temperature, 90°; helium flow rate, 70 ml min^{-1}; approximate authentic retention times (s): ATFA, 69; AcOH, 99; TFA, 136; Ac_2O, 159.



(a) TFA-DMAc at room temperature for 6 days.

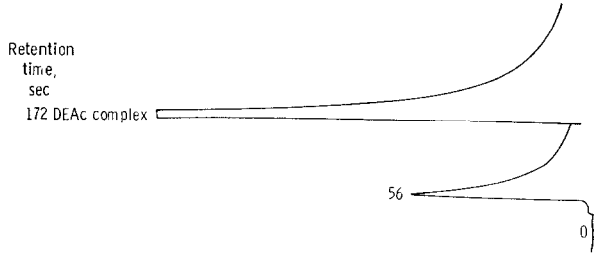


(b) TFA-DMAc at 180° to 153° C for 36 hours.

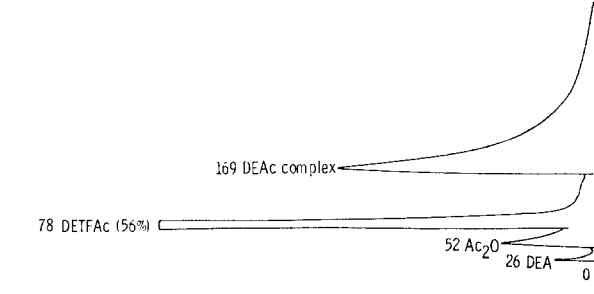
Fig. 7. Gas chromatographic analysis of

$$F_3CCOH + H_3CC\text{-}N(CH_3)_2 \longrightarrow F_3CC\text{-}N(CH_3)_2 + H_3CCOH.$$

Oven temperature, 120°; helium flow rate, 240 ml min^{-1}; approximate authentic retention times (s): AcOH, 30; TFA, 37; DMTFAc, 44; DMAc, 109.



(a) TFA-DEAc at room temperature for 24 hours.



(b) TFA-DEAc at 188° to 170° C for 24 hours.

Fig. 8. Gas chromatographic analysis of

$$F_3CCOH + H_3CC\text{-}N(C_2H_5)_2 \longrightarrow F_3CC\text{-}N(C_2H_5)_2 + H_3CCOH.$$

Oven temperature, 150°; helium flow rate, 85 ml min^{-1}; approximate authentic retention times (s): AcOH, 41; TFA, 46; Ac_2O, 54; DETFAc, 81; DEAc, 160.

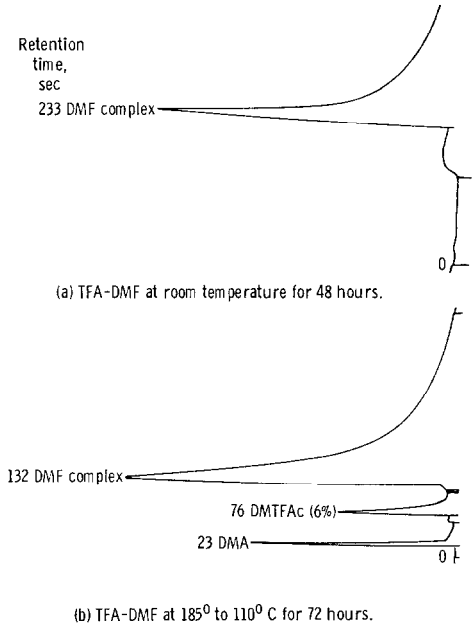


Fig. 9. Gas chromatographic analysis of

$$F_3CCOH + HC(=O)N(CH_3)_2 \longrightarrow F_3CC(=O)N(CH_3)_2 + H_2O + CO\uparrow.$$

Oven temperature, 110°; helium flow rate, 130 ml min^{-1}; approximate authentic retention times (s): TFA, 60; DMTFAc, 78; DMF, 121.

For the reaction of trifluoroacetic acid with *N,N*-dimethylacetamide under reflux conditions (Fig. 7(b)), as expected acetic acid was the sole by-product, but for *N,N*-diethylacetamide under reflux conditions (Fig. 8(b)) no peak for acetic acid was found; instead, peaks corresponding to acetic anhydride and diethylamine in relatively small peak area percentages were observed. The absence of an acetic acid peak in Figure 8(b) and also in Figure 3(b) suggests that it might form complexes with *N,N*-diethyltrifluoroacetamide. This is true; when *N,N*-diethyltrifluoroacetamide was mixed with 5–20 wt.% of acetic acid, the gas chromatographic results showed that most of the acetic acid was complexed and the remainder gave rise to peaks with longer retention times than the authentic value, being close to those of trifluoroacetic acid or acetic anhydride.

In the reaction of trifluoroacetic acid with *N,N*-dimethylformamide, *N,N*-dimethyltrifluoroacetamide was produced in low yield after the reaction mixture had been refluxed at 110–185° for 72 h (Fig. 9(b)). No water peak, however, was found during the gas chromatographic analysis, and the peak having a retention time of 23 s was dimethylamine not carbon monoxide. Dimethylamine might have resulted from the hydrolysis of the fluorinated amide formed since *N,N*-dimethyltrifluoroacetamide is even more susceptible to hydrolysis than *N,N*-dimethyl-

formamide[7]. Trifluoroacetic acid forms a constant boiling mixture with water containing 79.4% trifluoroacetic acid and having b.p. 105.5°[8]. We have found that trifluoroacetic acid and water (< 14 wt.%) cannot be separated from each other under the gas chromatographic conditions employed. A DMF complex with a retention time of 132 s (Fig. 9(b)) is formed from *N,N*-dimethylformamide, trifluoroacetic acid and water, while one with a longer retention time of 233 s (Fig. 9(a)) is formed by *N,N*-dimethylformamide and trifluoroacetic acid. Presumably, trifluoroacetic acid containing water will not readily protonate *N,N*-dimethylformamide, a low yield of product resulting.

It has been mentioned previously that fluorinated amides are generally more susceptible to hydrolysis than the non-fluorinated amides. A competitive hydrolysis of *N,N*-dimethylacetamide and *N,N*-dimethyltrifluoroacetamide was carried out in water (1.4:1.0:1.0 molar ratio) with acetone to form a homogeneous solution. After 50 days at room temperature, gas chromatographic analysis did not show any significant change in peak area ratio. When the mixture was refluxed at 112–140° for 22 h, dimethylamine was formed and the peak area ratio of *N,N*-dimethylacetamide to *N,N*-dimethyltrifluoroacetamide increased from 44.7:46.8 (or 0.95) to 73.5:21.6 (or 3.4) (Fig. 10) confirming that trifluoroacetamide is more susceptible to hydrolysis.

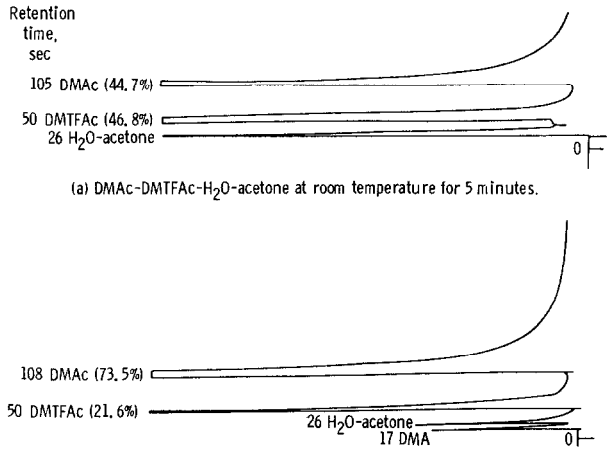
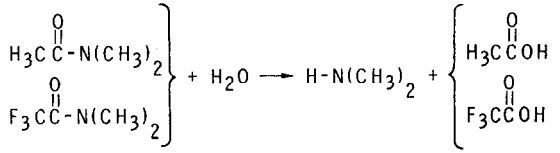


Fig. 10. Gas chromatographic analysis of



Oven temperature, 120°; helium flow rate, 240 ml min^{-1}; approximate authentic retention times (s): H_2O–acetone, 26; AcOH, 30; TFA, 37; DMTFAc, 44; DMAc, 109.

EXPERIMENTAL

Analytical gas–liquid chromatograph

All analyses were performed using a 1.8 m long and 6 mm diameter copper tubing column packed with 15% Dow Corning 200 silicone oil on 60/80 mesh Chromosorb W at oven temperatures and helium flow rates designated on the figures. Retention times of the authentic components involved were obtained separately under corresponding chromatographic conditions.

General procedure for the syntheses of N,N-*dialkyltrifluoroacetamides*

Into a 200 or 500 ml 3-neck round-bottom flask fitted with a magnetic stirrer, gas inlet, thermometer, a graduated pressure equalizing separatory funnel and a condenser cooled at about −20°, 0.1 to 0.5 mole of trifluoroacetic anhydride or trifluoroacetic acid was introduced and covered with a blanket of dry nitrogen gas. From the funnel, an equimolar amount of *N,N*-dialkyl-formamide or -acetamide was slowly added with stirring and occasional cooling to control any exothermic reactions. When all the amide had been added and the exotherm had subsided, the reaction mixture was heated to and held at reflux until gas chromatographic analysis showed that the trifluoroacetic anhydride or acid peaks had nearly disappeared or that an equilibrium had been established. The reaction mixture was fractionated with a spinning-band distillation apparatus at atmospheric pressure. *N,N*-Dimethyltrifluoroacetamide was collected at 130–134° and *N,N*-diethyltrifluoroacetamide at 157–160°. Yields were 70–90% (based on *N,N*-dialkyl-formamide or -acetamide) for all the reactions except trifluoroacetic acid–*N,N*-dimethylformamide (less than 10%). No special effort was made to optimize reaction conditions for maximum yields. Infrared spectrophotometry was also used to identify the products[9].

Equilibria of mixed anhydride and anhydride–acid systems involving acetyltrifluoroacetate

In a similar set-up to that described above (100 ml flask), 0.05 mole of trifluoroacetic anhydride or trifluoroacetic acid was covered with a blanket of dry nitrogen gas. An equimolar amount of acetic anhydride or acid was added slowly from the funnel so that the reaction mixture was kept below room temperature with only occasional cooling with cold water. After the reactants had been added and the exotherm subsided, the solution was brought to room temperature and a sample taken for gas chromatographic analysis. The reaction mixture was then transferred to a glass bottle and stored at room temperature. Gas chromatographic analyses were performed repeatedly after appropriate intervals of time until the reaction mixture reached equilibrium.

Competitive hydrolysis of N,N-*dimethylacetamide and* N,N-*dimethyltrifluoroacetamide*

A homogeneous solution was obtained at room temperature by mixing 0.0224 mole (1.943 g) of *N,N*-dimethylacetamide, 0.0158 mole (2.237 g) of *N,N*-dimethyltrifluoroacetamide and 0.0158 mole (0.3 ml) of water with acetone (1:1 by volume). A sample of the mixture was taken for gas chromatographic analysis at 120° and a helium flow rate of 240 ml min^{-1}. About 90% of the mixture was refluxed at 112–140° for 22 h, while the remaining 10% was kept at room temperature for 50 days prior to further gas chromatographic analysis.

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APPENDIX

Abbreviations used in the figures:

Ac_2O	acetic anhydride
AcOH	acetic acid
ATFA	acetyltrifluoroacetate
DEA	diethylamine
DEAc	*N,N*-diethylacetamide
DETFAc	*N,N*-diethyltrifluoroacetamide
DMA	dimethylamine
DMAc	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMTFAc	*N,N*-dimethyltrifluoroacetamide
R	CH_3, C_2H_5
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride