Synthesis of Multifunctional Triarylfluoroethanes. 1. Condensation of Fluoro Ketones

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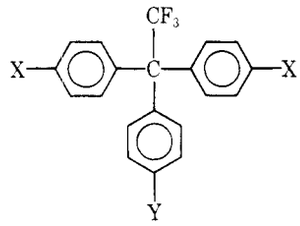
A convenient method for the preparation of 1,1,1-triaryl-2,2,2-trifluoroethanes is reported. α,α,α-Trifluoroacetophenones are condensed with aromatic substrates in the presence of trifluoromethylsulfonic acid.

As part of our investigations on the synthesis of new polyfunctional monomers, we now wish to report a convenient method for the preparation of the previously unreported 1,1,1-triaryl-2,2,2-trifluoroethanes of the type **1**.



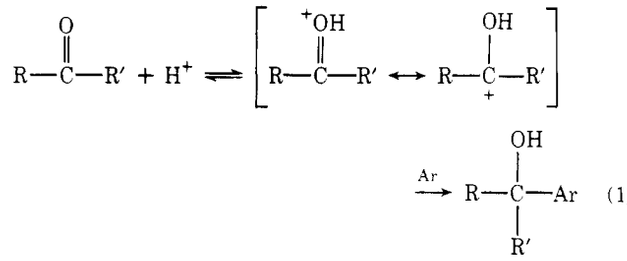
1

X = NH_2, CH_3, COOH, CHO, C≡N
Y = X, H

While the literature is replete with numerous examples of polyfunctional triarylmethanes and carbinols, compounds of the type **1** have not been described. The corresponding trichloride has been mentioned,[2] but the method used would not lend itself toward large-scale preparation, nor was it directly applicable to the synthesis of the desired fluorinated analogues.

The method that we chose was a modified hydroxyalkylation of the appropriate trifluoroacetophenones. The literature has numerous examples of hydroxylalkylation.[3-5] In all cases, a ketone or an aldehyde is protonated with an acid catalyst, and the resulting "ion" acts as an electrophile for aromatic substitution (eq 1). In some cases, further reaction may occur by acid-catalyzed dehydration of the intermediate carbinol to a carbonium ion and subsequent aromatic substitution.

The reaction of fluoro ketones with a variety of aromatic substrates has been reported;[6-8] however, the reaction either stopped at the carbinol stage or gave further reaction only when the carbonyl compound was an aldehyde or a perfluoroalkyl ketone. Until now no examples of acid-catalyzed condensations of trifluoroacetophenones with aromatic substrates to give 1,1,1-triaryl-2,2,2-trifluoroethanes have been reported.

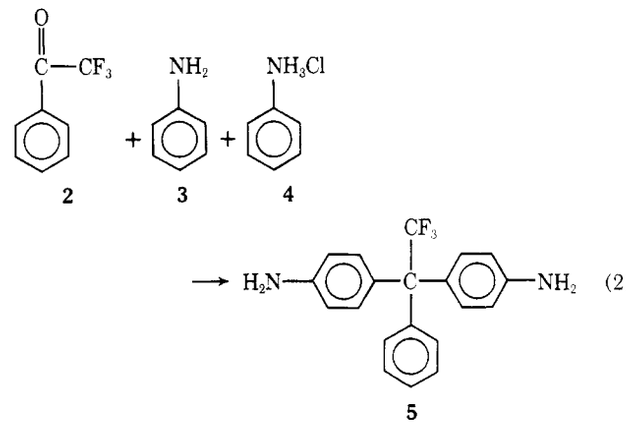


(1)

The method used for the preparation of the title compounds was a modification of the procedure developed by Patai and Dayagi[9] and Baeyer–Villiger[10] to prepare 1,1,1-tris(4-aminophenyl)methane derivatives from substituted aldehydes.

Results and Discussion

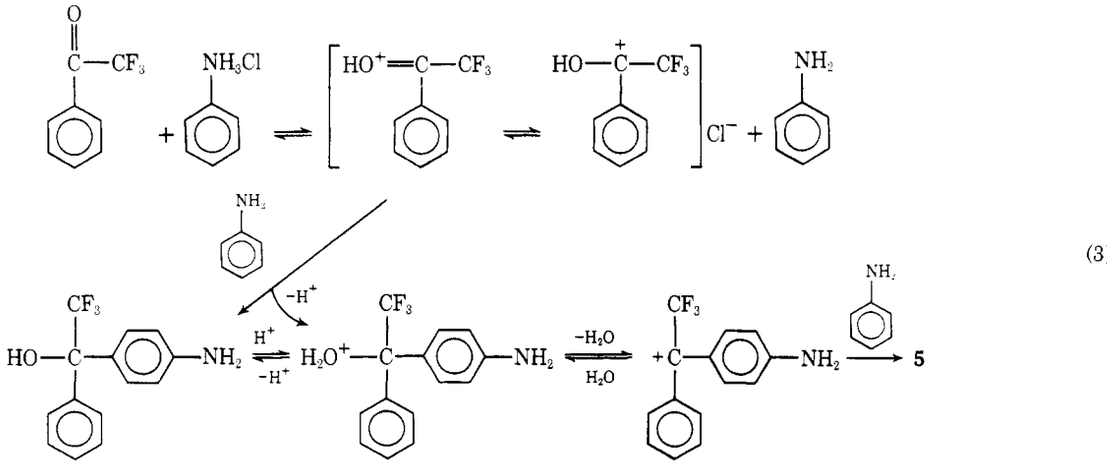
When trifluoroacetophenone **2** was refluxed with aniline **3** and aniline hydrochloride **4**, the desired 1,1-bis(4-aminophenyl)-1-phenyl-2,2,2-trifluoroethane (**5**) was isolated in good yield (eq 2). The product was accompanied by a deep



2 **3** **4**

(2)

5

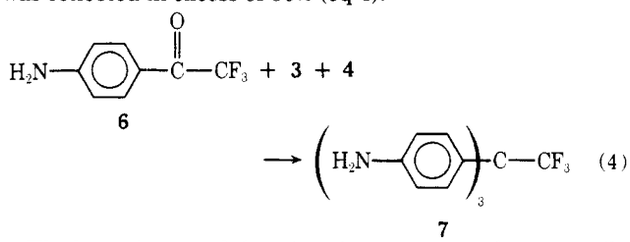


(3)

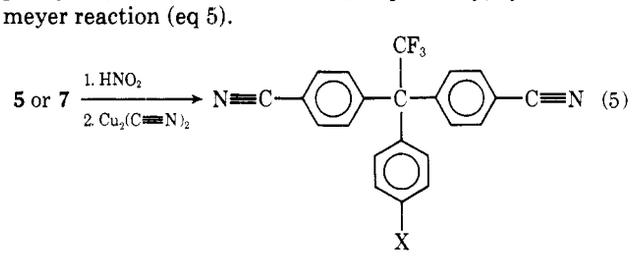
blue, uncharacterized by-product which was easily absorbed on a column of silica gel. The mechanism of the reaction can be postulated to be a typical hydroxyalkylation condensation as illustrated in eq 3.

It was found that the amount of aniline hydrochloride was not critical. A catalytic amount was required (sufficient), but insufficient amounts resulted in longer reaction times and greater amounts of the blue by-product. Forcing conditions using a Dean-Stark trap did not increase the yield. Spectral analysis of the diamine **5** indicated that only para substitution of the aniline occurred, as the NMR of the amine or amide gave a clear singlet for the unsubstituted phenyl ring and a clean pair of doublets for the para-substituted rings.

The condensation was extended to the reaction of 4-aminotrifluoroacetophenone (**6**)[12] with aniline under similar conditions and once again the yields were very good. The product, 1,1,1-tris(4-aminophenyl)-2,2,2-trifluoroethane (**7**) was collected in excess of 50% (eq 4).



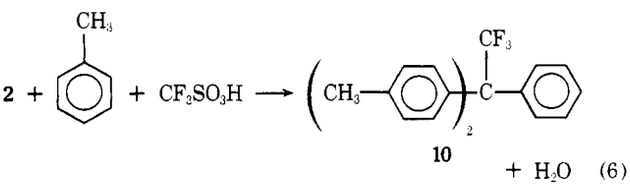
The bisamino **5** and the trisamino **7** compounds were easily converted to the corresponding 1,1-bis(4-cyanophenyl)-1-phenyl-2,2,2-trifluoroethane (**8**) and the 1,1,1-tris(4-cyanophenyl)-2,2,2-trifluoroethane (**9**), respectively, by the Sandmeyer reaction (eq 5).



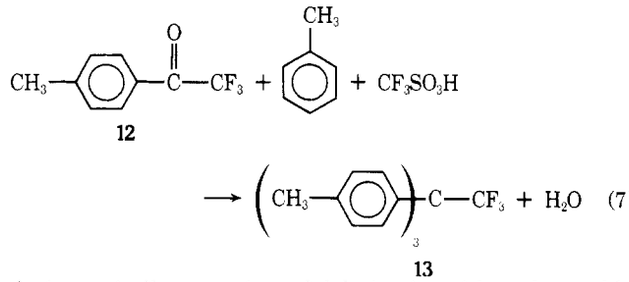
when X = H, **8**
X = C≡N, **9**

In order to study the condensation of 2,2,2-trifluoroacetophenone with other aromatic substrates, a variety of conditions were explored. First, the condensation of trifluoroacetophenone with toluene was attempted. Since aniline hydrochloride was inappropriate in this case, the employment of another nonvolatile acid was necessary. A variety of acids were tried (H_2SO_4, H_3PO_4, and polyphosphoric acid), but in all cases negative results were obtained. When sulfuric acid was used in refluxing toluene, a solid product was obtained. The product collected was the desired 1,1-bis(*p*-tolyl)-1-phenyl-2,2,2-trifluoroethane (**10**) plus large amounts of ditolyl sulfone **11**. Workup conditions removed any *p*-toluenesulfonic acid.

Numerous recrystallizations and/or column separations failed to completely remove the sulfone from the desired product **10**; however, when trifluoroacetophenone was refluxed with toluene and trifluoromethylsulfonic acid (TMSA), it was possible to isolate the desired product **10** in a 50% yield. The remainder of the solid product was a brown tar which was not characterized (eq 6).



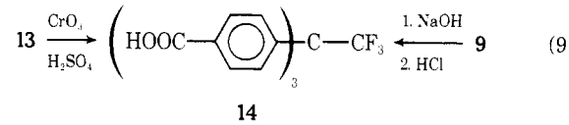
Similarly when 4-methyl-α,α,α-trifluoroacetophenone (**12**)[13] was refluxed with TMSA in toluene, 1,1,1-tris(*p*-tolyl)-2,2,2-trifluoroethane (**13**) was isolated in a 50% yield (eq 7). The NMR and IR analyses indicated that the product was



the isomerically pure tri-*p*-tolyl derivative with no detectable amounts of the ortho isomer. This is not unexpected as one would postulate that the electrophile (protonated ketone) is very bulky and any ortho substitution would be sterically unfavorable.

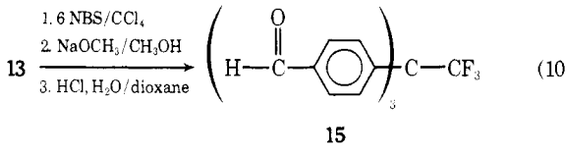
The structure **13** was easily converted in high isolated yield (80%) to the corresponding tricarboxylic acid **14** by chromic oxide oxidation.

The trinitrile **9** was also readily converted to the triacid **14**



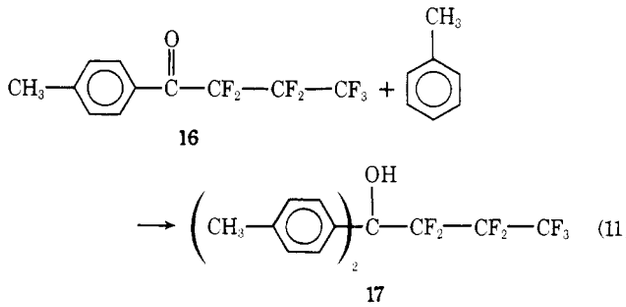
by simple base hydrolysis and acidification of the resulting aqueous solution, thus rendering additional proof as to the structure of the trinitrile.

One compound of interest was the trisformyl derivative **15.** One possible route for obtaining **15** was reduction of the trinitrile **9** to an imine with subsequent hydrolysis. This pathway was not tried because the synthesis of trinitrile was long and difficult. Another possible route to the triformyl compound would utilize the tristolyl derivative **13,** and because this material was more readily available, it was chosen as the starting point. Crude 1,1,1-tris(4-formylphenyl)-2,2,2-trifluoroethane (**15**) was prepared by bromination of **13** to the hexabromide, followed by conversion of the dimethyl acetal and subsequent hydrolysis (eq 10).



The triformyl compound **15** was purified by column chromatography. Subsequent thin layer analysis of the waxy semisolid gave one spot.

One rather interesting point is that apparently aryltrifluoromethyl ketones are unique for the above hydroxyalkylation. When 4-methylheptafluorobutyrophenone (**16**) was refluxed with toluene and trifluoromethylsulfonic acid, the alcohol (di-*p*-tolyl-*n*-heptafluoropropylcarbinol) **17**[4] was isolated from the tarry reaction product.



The condensation of trifluoroacetophenone with other aromatic substrates was attempted and anomalous results were obtained. For example, when trifluoroacetophenone and ethylbenzene were refluxed with trifluoromethylsulfonic acid, a mixture of products was obtained. Initial studies indicate that the ethyl group is involved in some secondary process.

In conclusion, we have demonstrated that that selected trifluoroacetophenones can undergo hydroxyalkylation reactions with selected acids. The products obtained are the previously unreported 1,1,1-triaryl-2,2,2-trifluoroethanes. The product yield ranged from good to excellent. Further studies are in progress and will be reported later.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. IR and NMR spectra were taken on a Perkin-Elmer 180 and Varian HA-100, respectively. Mass spectra were obtained on a Bell and Howell-21-491 at 70 eV. Elemental analyses were performed by I. J. Wilk, Palo Alto, Calif.

1,1-Bis(4-aminophenyl)-1-phenyl-2,2,2-trifluoroethane (See 5, Eq 2). A mixture of 10 g (0.057 mol) of trifluoroacetophenone **2**, 0.43 mol of aniline, and 10 g (0.078 mol) of aniline hydrochloride was refluxed for 24 h. At the end of the reflux period, 10 g (0.12 mol) of sodium bicarbonate was added and the mixture steam distilled until the distillate was clear. The aqueous solution was cooled and the solid, dark-blue residue was broken up and collected. The residue was dissolved in benzene, dried over anhydrous magnesium sulfate, passed through a silica gel column (approximately five times the weight of solid material was used), and eluted with benzene. The dark-blue impurity remained in a band at the top of the column. The benzene was removed on a rotary evaporator, and the remaining solid was recrystallized from benzene and petroleum ether (petroleum ether was added to a hot benzene solution) to give 17.3 g (88% from the ketone) of rose-colored crystals: mp 201–204 °C; IR ($CHCl_3$) 3450 and 3380 (NH_2), 1610 and 1500 (Ar), 1140 cm^{-1} (C–F); IR (KBr) 825 (para-disubstituted Ar), 760 and 710 cm^{-1} (monosubstituted Ar); NMR δ 3.55 (s broad, 4 H), 6.58 (d, 4 H), J = 5 Hz), 6.88 (d, 4 H, J = 5 Hz), 7.28 (m, 5 H); mass spectrum m/e 342 (parent ion), 273 (P − 69, base peak), 195 (P − 147), 180 (P − 167).

1,1-Bis(4-acetamidophenyl)-1-pheny-2,2,2-trifluoroethane. Five grams (0.015 mol) of the diamine **5** was added, with stirring, to 5 ml of hot acetic anhydride. The diamine dissolved instantaneously, the resulting solution was cooled, and the white precipitate was collected. The product was crystallized from aqueous ethanol giving 4.99 g (79% from the diamine) of white crystals: mp 255–256 °C; NMR δ 2.08 (s, 6 H), 7.04 (d, 4 H), J = 4.5 Hz, 7.28 (m, 5 H), 7.62 (d, 4 H, J = 4.5 Hz); mass spectrum m/e 426 (parent ion), 357 (P − 69 base peak), 315 (P − 111), 273 (P − 153), 180 (P − 246). Anal. Calcd for $C_{24}H_{21}N_2O_2F_3$: C, 67.60; H, 4.92; N, 6.57; F, 13.38. Found; C, 67.61; H, 4.92; N, 6.49; F, 14.1.

1,1-Bis(4-cyanophenyl)-1-phenyl-2,2,2-trifluoroethane (8). Four grams (0.011 mol) of the diamine **5** was slowly added, with constant stirring, to 5 ml of concentrated hydrochloric acid and 20 ml of water. The solution was cooled to 0 °C with an ice bath, and 1.8 g (0.024 mol) of sodium nitrite (in 10 ml of water) was added dropwise over a 30-min period. The solution was carefully neutralized (pH meter) with anhydrous sodium carbonate. The carbonate addition was accompanied by extensive foaming, so extra-large vessels were used. When the solution was neutralized, it was slowly added to a freshly prepared solution of cuprous cyanide,[11] made from 15 g (0.15 mol) of chloride and 21.8 g (0.3 mol) of sodium cyanide in 200 ml of cold water. The temperature of reaction was maintained at 0–5 °C by external cooling. The cyanide solution was allowed to warm to room temperature over a 2-h period, then warmed on a steam bath for 30 min. The solution was cooled to room temperature and extracted three times with 100-ml portions of chloroform. The chloroform extracts were combined and dried over magnesium sulfate, and the chloroform was removed on a rotary evaporator. The resulting oil was dissolved in hot ethanol, and water was added until the solution became slightly turbid. Upon cooling, a dark oil separated. The solution was decanted and reheated and more water added until the solution was turbid. The hot solution was allowed to cool very slowly. The resulting pale yellow crystals, 1.8 g (46%), mp 169–172 °C, were collected: IR (KBr) 2230 (C≡N), 1610 and 1510 (Ar), 1100 (C–F), 860 (para-disubstituted Ar), 760 and 720 cm^{-1} (monosubstituted Ar); NMR δ broad m (quartet 7.2–7.8); mass spectrum m/e 362 (parent ion), 293 (P − 69, base peak), 215 (P − 147), 190 (P − 172). Anal. Calcd for $C_{22}H_{13}N_2F_3$: C= 73/74: H, 3.63; N, 7.82; F, 15.92. Found: C, 73.76; H, 3.72; N, 7.49; F, 16.0.

1,1,1-Tris(4-aminophenyl)-2,2,2-trifluoroethane (7). The title compound was prepared in the same manner as the diamino derivative. A mixture of 47 g (0.25 mol) of 4-aminotrifluoroacetophenone,[12] 50 g (0.38 mol) of aniline hydrochloride, and 200 ml of aniline was refluxed for 24 h and worked up in the usual manner to give 49 g (57%) of tan crystals, mp 186–190 °C.

1,1,1-Tris(4-acetamidophenyl)-2,2,2-trifluoroethane. Two grams (0.0056 mol) of the triamine was acetylated in the same manner as the diamine to yield 1.74 g (65% yield) of white crystals: mp 343–345 °C; IR ($CHCl_3$) 3300 (NH), 1710 (C=C), 1620 and 1515 (Ar), 1140 (C–F), 830 cm^{-1} (para-disubstituted phenyl); NMR δ 2.05 (s, 9 H), 7.05 (d, 6 H, J = 5 Hz), 7.65 (d, 6 H, J = 5 Hz). Anal. Calcd for $C_{26}H_{24}N_3O_3F_3$: C, 64.59; H, 4.96; N, 8.69; F, 11.80. Found: C, 63.92; H, 5.20; N, 7.98; F, 11.50.

1,1,1-Tris(4-cyanophenyl)-2,2,2-trifluoroethane (9). The title compound was prepared in the same manner as the dicyano derivative. Fifty grams of 1,1,1-tris(4 aminophenyl)-2,2,2-trifluoroethane (0.14 mol) was diazotized and treated, at pH 7, with cuprous cyanide. The yield was 24 g (44%) of pale yellow crystals: mp 233–235 °C; IR ($CHCl_3$) 2230 (–C≡N), 1600 and 1490 (Ar), 1140 (C–F), 830 cm^{-1} (para-disubstituted Ar); NMR δ 7.21 (d, J = 11 Hz), 7.72 peak (d, J = 11 Hz); mass spectrum m/e 387 (parent ion), 318 (P − 69, base peak), 289 (P − 98), 215 (P − 172). Anal. Calcd for $C_{23}H_{12}N_3F_3$: C, 70.31; H, 3.10; F, 14.72. Found: C, 70.75; H, 3.40; F, 14.3.

1-Phenyl-1,1-bis(*p*-tolyl)-2,2,2-trifluoroethane (10). A mixture of 10 g (0.057 mol) of trifluoroacetophenone, 100 ml of toluene, and 5 ml of trifluoromethylsulfonic acid was refluxed, under a Dean-Stark trap, for 48 h. At the end of this period, the mixture was cooled, transferred to a separatory funnel, and extracted with water (100 ml), saturated sodium bicarbonate (100 ml), and water (100 ml), then dried with magnesium sulfate. Excess toluene was removed on a rotary evaporator and the dark brown oil dissolved in petroleum ether/benzene (500 ml) (50/50 v/v). The resulting solution was passed through a silica gel column (50 g) leaving a dark band at the top of the column, and the column then washed with 500 ml of additional solvent. The fractions were combined, solvent removed, and the product crystallized from aqueous ethanol. The crystals were washed with ethanol to give 9.0 g (43%) of white crystals: mp 168–169 °C; IR (KBr) 1590 and 1495 (Ar), 1145 (C–F), 810 (para-substituted phenyl), 740 and 690 cm^{-1} (monosubstituted phenyl); NMR δ 2.15 (s, 6 H), 6.90 (s, 13 H); mass spectrum m/e 340 (parent ion), 271 (P − 69, base peak), 194 (P − 146), 193 (P − 147), 180 (P − 160), 179 (P − 161). Anal. Calcd for $C_{22}H_{19}F_3$: C, 77.64; H, 5.58; F, 16.76. Found: C, 78.07; H, 5.55; F, 16.4.

1,1,1-Tris(*p*-tolyl)-2,2,2-trifluoroethane (13). A solution of 10 g (0.056 mol) of 4-methyltrifluoroacetophenone[8] in 100 ml of toluene and 5 ml of trifluoromethylsulfonic acid was refluxed for 48 h and worked up in the same manner as **10** to yield 11.2 g (56%) of white crystals: mp 217–218 °C; IR (KBr) 1605 and 1500 (Ar), 1150 (C–F), 805 cm^{-1} (para-substituted Ar); NMR δ 2.15 (s, 3 H), 6.9 (s, 4 H); mass spectrum m/e 354 (parent ion), 285 (P − 69, base peak), 194 (P − 160), 193 (P − 161), 178 (P − 176). Anal. Calcd for $C_23H_{21}F_3$: C, 77.96; H, 5.93; F, 16.10. Found: C, 78.15; H, 5.99; F, 15.8.

1,1,1-Tris(4-carboxyphenyl)-2,2,2-trifluoroethane (14). Two grams (0.0056 mol) of the tritolyl trifluoroethane **13** was added over a 30-min period to a cooled solution of 8.4 g (0.084 mol) of chromium trioxide in 67 ml of acetic acid, 22 ml of acetic anhydride, and 5.5 ml of sulfuric acid. The temperature of the solution was maintained at 10–15 °C for 2 h. The resulting brown-green solution was poured into 600 ml of ice water and stirred overnight. The product was collected on a Büchner funnel and dried under vacuum overnight to yield a pale green solid. The solid material was transferred to a Soxhlet thimble and extracted with a benzene–1,2-dimethoxyethane solution (80/20 v/v) for 24 h. The solution was cooled and triturated with light petroleum ether. The white powder was collected and air dried to yield 1.80 g: mp 366–367 °C; IR (KBr) 3440 (very broad), 1690, 1570, and 1415 (COOH), 1605 and 1510 (Ar), 1150 (C–F), 810 cm^{-1} (para-substituted phenyl). Anal. Calcd for $C_{23}H_{15}O_6F_3$: C, 62.16; H. 3.37; F, 12.83. Found: C, 61.99; H, 3.40; F, 13.0.

1,1,1-Tris(4-formylphenyl)-2,2,2-trifluoroethane (15). A mixture of 1.00 g (0.0028 mol) of 1,1,1-tris(*p*-tolyl)-2,2,2-trifluoroethane, 3.1 g of *N*-bromosuccinimide (0.017 mol, 6.22 equiv), and 100 mg (approximate) of benzoyl peroxide in 25 ml of carbon tetrachloride was refluxed for 6 h, or until all of the heavier NBS (NBS *d*, 2.098; CCl_4 *d*, 1.5940) was entirely consumed and the lighter (*d* 1.4180) succinimide floated on the surface of the solution. The product was filtered and the carbon tetrachloride evaporated under anhydrous conditions to give the desired hexabromide which was used without purification in the next step.

A solution made from dissolving 0.58 g (0.02 mol) of sodium in 50 ml of anhydrous methanol was added to the hexabromide and the mixture refluxed for 2 h. At the end of the refluxing period, the solution was filtered and solvent removed in vacuo to yield an oil which solidified overnight. The residue was dissolved in 25 ml of dioxane, and 75 ml of water and 5 ml of concentrate hydrogen chloride were added to the stirring solution. The resulting cloudy mixture was stirred at room temperature overnight. After the hydrolysis was complete the aqueous solution was extracted three times with 50-ml portions of ether, dried with anhydrous magnesium sulfate, and evaporated to yield a pale yellow solid. The NMR spectrum of the crude mixture has singlets at δ 4.45 and 3.42, indicating the presence of a $ArCH_2OCH_3$ group. Integration of the mixture indicated that the product was approximately 90% pure trialdehyde. Column chromatography of the mixture gave 0.59 g of material approximately 90% pure, the major contaminant being a methyl ether resulting from incomplete bromination. The following data were determined: IR ($CHCl_3$) 2840 and 2740 (CHO), 1710 (C=O), 1610 and 1510 (Ar), 1140 (C–F), 810 cm^{-1} (para-substituted Ar); NMR δ 7.3 (d, J = 8 Hz), 7.84 (d, J = 8 Hz), 10.04 (s).

Registry No.—**2**, 434-45-7; **3**, 62-53-3; **5**, 61204-04-4; **6**, 23516-79-2; **7**, 61204-05-5; **8**, 61204-06-6; **9**, 61204-07-7; **10**, 61204-08-8; **12**, 394-59-2; **13**, 61204-09-9; **14**, 61204-10-2; **15**, 61204-11-3; 1,1-bis(4-acetamidophenyl)-1-phenyl-2,2,2-trifluoroethane, 61204-12-4; acetic anhydride, 108-24-7; cuprous cyanide, 544-92-3; 1,1,1-tris(4-acetamidophenyl)-2,2,2-trifluorothane, 61204-13-5; toluene, 108-88-3; trifluoromethylsulfonic acid, 1493-13-6.

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A Synthetic Route to Highly Substituted Ketones. Acylations of α Anions of Carboxylic Acid Salts with Acid Chlorides[1]

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A versatile synthetic route leading to highly substituted ketones has been developed. Treatment of disubstituted α-lithiated carboxylic acid salts **2** with acyl chlorides leads to the diisopropylammonium salts of the β-keto acids **4**. Thermolysis of these isolated salts produces excellent yields of ketones. In particular, this procedure is useful for the synthesis of symmetrical and unsymmetrical dicycloalkyl ketones. The α anion derived from phenylacetic acid on treatment with acyl chlorides and acidic workup leads directly to ketones in good yield. The α anions derived from acetic acid and propionic acid lead to poor yields of ketones on treatment with acyl chlorides.

Carboxylic acids with aryl or olefinic substituents attached to the α carbon produce "Ivanov" reagents on treatment with Grignard reagents, and many useful synthetic applications of these reagents have been reported.[4] Although α anions derived from salts of aliphatic carboxylic acids have been known for about 40 years,[5] the preparative difficulties have only been recently resolved. These α anions can conveniently be prepared by treatment of alicyclic or aliphatic carboxylic acids with 2 equiv of nonnucleophilic bases such as lithium diisopropylamide (LDA) in solvents like THF.[6] Various researchers have utilized alkali metal radical anions to generate α anions.[7]

The goal of the present research was to explore the reaction of α anions derived from readily available aliphatic and alicyclic carboxylic acid salts with acyl chlorides as a synthetic route to ketones. Two related studies which lead to ketones have been recently described. Treatment of α anions of carboxylate salts with a few esters followed by addition of TMCS leads to β-keto acid trimethylsilyl esters which can be methanolyzed to the β-keto acids and then converted into ketones.[8] Angelo treated α anions (generated from acids with lithium naphthalenide) with esters to produce β-keto acids. The β-keto acids derived from acetic acid could be isolated in good yields, but no β-keto acids could be isolated from mono- or disubstituted carboxylic acids; these acids also led to poor yields of ketones.[7c]

In related studies, α anions derived from esters have been treated with acyl chlorides to yield β-keto esters.[6c,9]

The conversion of carboxylic acid derivatives such as acyl halides to simple and highly substituted ketones using organometallics as alkyl transfer agents[10a-i] and organo derivatives of silicon[11] and boron[12] has been reported. Carboxylate salts have been treated with organometallic reagents to form ketones.[10j,k] Acids have been converted into dihydro-1,3-oxazines[13] and 4,4-dimethyl-2-oxazolines[14,15] and treatment of these heterocycles with 2 equiv of organolithium reagents followed by hydrolysis, or by subsequent addition of an alkyl halide followed by hydrolysis, leads to highly substituted ketones.

Results and Discussion

We wish to report a convenient two-step synthetic procedure in which acid chlorides are treated with carboxylic acids to produce ketones via the following formal transformation:

$$R_1R_2CHCOOH + R_3COCl \rightarrow R_1R_2CHCOR_3$$