# Preparation of α-Trifluoromethyl Esters from Malonic Esters[1]

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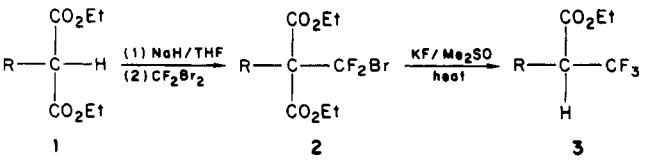
A wide variety of α-trifluoromethyl esters can be synthesized in two steps starting from monosubstituted malonic esters and dibromodifluoromethane. The product of the first step, a bromodifluoromethyl-substituted malonate, is transformed to the desired final product by use of KF in $Me_2SO$ at elevated temperatures. This second step involves both the loss of one ester and halogen exchange and proceeds through an α,β-unsaturated ester in which two fluorine atoms are bonded to the terminal carbon.

Selective fluorination of organic molecules now rivals, or may even surpass perfluorination as the major interest of researchers involved in organofluorine chemistry. Because of the unique character of the fluorine atom both areas have as a goal the synthesis of compounds with special chemical and physical properties. Recently significant progress has been made to allow easier incorporation of fluorine at a wide variety of sites in an organic compound. Concern for safe handling and use has directed attention to alternatives to the toxic and reactive reagents characteristic of past work in fluorine chemistry and a main obstacle to the common use of such methods. Reagents such as *N*-fluoropyridone[2a] and *N*-fluorosulfonamides[2b] can now be used instead of perchloryl fluoride and similar, highly sensitive compounds for the monofluorination of many organic substrates. Geminal difluorinated molecules can be readily obtained using DAST[3] ((diethylamino)sulfur trifluoride), a more selective and controllable reagent than sulfur tetrafluoride, from which it is derived.

New methods have also appeared for the synthesis of compounds containing the trifluoromethyl group in response to increased interest in this unit which imparts special electronic effects and increased lipophilicity.[4] Biomedical use of trifluoromethylated drugs and metabolic probes is but one of the many applications of selectively fluorinated organic molecules.[5] Previous multistep processes are being supplanted by more direct routes, although a $CF_3^+$ intermediate or its equivalent still remains elusive. Trifluoromethyl iodide and trifluoromethyl triflate[6] do not act as sources of $CF_3^+$, since nucleophiles attack the iodine of $CF_3I$ and the sulfur of $CF_3OSO_2CF_3$. FITS reagents[7] (perfluoroalkyl phenyliodonium trifluoromethanesulfonates) allow perfluoroalkylation of organic compounds but require $R_f$ to have two or more carbon atoms, excluding the use of these reagents for transfer of the $CF_3$ moiety.

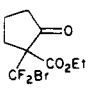
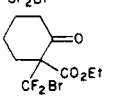
Some of the most useful trifluoromethylation reactions employ organometallic reagents—trifluoromethyl copper[8] or zinc[9] complexes. But the analogous Grignard reagent, $CF_3MgX$, is difficult to prepare and gives low yields of trifluoromethylated product.[10] Clearly, there is a need for finding new, generally applicable synthetic methods for incorporation of $CF_3$ groups.

We have developed a simple two-step synthesis of esters containing a trifluoromethyl group in the α-position[11] by modifying the familiar pathway of malonic ester synthesis. This sequence begins with monosubstituted diethyl malonates. The first step involves the generation of a malonate nucleophile, which reacts with $CF_2Br_2$ to give the bromodifluoromethyl-substituted malonate. This product




1 2 3

**Table I. Yields of Bromodifluoromethylated Compounds[a]**

| no. | R or β-keto ester | % yield[b] | bp, °C/mmHg | $^{19}F$ NMR,[c] δ |
|---|---|---|---|---|
| **2a** | Me | 76 | 66/0.2 | 50 (s) |
| **2b** | Et | 73 | 90/0.3 | 47 (s) |
| **2c** | *n*-Pr | 74 | 82/0.2 | 47 (s) |
| **2d** | *n*-Bu | 66 | 95/0.3 | 47 (s) |
| **2e** | $CH_2CH{=}CH_2$ | 68 | 80/0.2 | 47 (s) |
| **2f** | $CH_2CH_2CN$ | 80 | 118/0.3 | 48 (s) |
| **2g** | $CO_2Et$ | 14 | 104/0.3 | 48 (s) |
| **2h** | $CH_2CO_2Et$ | 53 | 108/0.2 | 49 (s) |
| **2i** | $C_6H_5$ | 85 | 124/0.3 | 47 (s) |
| **2j** | $CH_2C_6H_5$ | 75 | 122/0.3 | 47 (s) |
| **2k** | $NHCOCH_3$ | 1 | mp 56 | 52 (s) |
| **2l** |  | 5 | 90/0.3 | 50 (s) |
| **2m** |  | 3 | 120/0.4 | 50 (s) |

[a] Reaction conditions: **2a–e**, stir overnight at room temperature; **2f–m**, stir 8–12 days at room temperature. Satisfactory analytical data were obtained for all new compounds listed in the table, with the exception of **2g**. Analysis of this compound was not satisfactory, even though GC indicates 98+% purity. Methanetricarboxylates readily undergo dealkoxycarbonylation (Padgett, H. C.; Csendes, I. G.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 3492). With a fourth electron-withdrawing group attached to the central carbon, **2q** is even less stable. [b] Isolated yields (90+% pure by GC). [c] ppm downfield from $CFCl_3$.

(1) Preliminary results of this study were reported: *Tetrahedron Lett.* **1984**, *25*, 1329.

(2) (a) Purrington, S. T.; Jones, W. A. *J. Org. Chem.* **1983**, *48*, 761. Purrington, S. T.; Jones, W. A. *J. Fluorine Chem.*, in press. (b) Barnette, W. E. *J. Am. Chem. Soc.* **1984**, *106*, 452.

(3) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

(4) Patrick, T. B. *J. Chem. Ed.* **1979**, *56*, 228.

(5) (a) Filler, R., Ed. *ACS Symp. Ser.* **1976**, No. 28. (b) Filler, R.; Kobayashi, Y., Ed. "Biomedicinal Aspects of Fluorine Chemistry"; Kodansha Ltd.: Tokyo; Elsevier Biomedical Press: New York, 1982.

(6) Kobayashi, Y.; Yoshida, T.; Kumadaki, I. *Tetrahedron Lett.* **1979**, 3865.

(7) Umemoto, T.; Kuriu, Y.; Shuyama, H.; Miyano, O.; Nakayama, S. *J. Fluorine Chem.* **1982**, *20*, 695.

(8) Kobayashi, Y.; Yamamoto, K.; Kumadaki, I. *Tetrahedron Lett.* **1979**, 4071.

(9) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1982**, 137.

(10) Hudlicky, M. "Chemistry of Organic Fluorine Compounds: A Laboratory Manual"; Ellis Horwood: New York, 1976.

(11) Silyl ketene acetals, prepared from β,β,β-trifluoropropionate, react with electrophiles to give a series of α-trifluoromethyl esters complementary to the ones reported here. Nakai, T.; Yokozawa, T.; Ishikawa, N. "Abstracts of Papers", 186th National Meeting of the American Chemical Society, Washington, D.C., Aug 28–Sept 2, 1983. FLUO 24

0022-3263/84/1949-3702$01.50/0 

Table II. Yields of α-Trifluoromethyl Esters[a]

| no. | R | % yield[b] | bp, °C/mmHg | $^{19}F$ NMR,[c] δ |
|---|---|---|---|---|
| **3a** | Me[d] | 44 | 112 | 71 (d) |
| **3b** | Et | 44 | 128 | 69 (d) |
| **3c** | *n*-Pr | 40 | 145 | 69 (d) |
| **3d** | *n*-Bu[e] | 34 | 163 | 69 (d) |
| **3e** | $CH_2CH{=}CH_2$ | 44 | 143 | 69 (d) |
| **3f** | $CH_2CH_2CN$ | 35 | 60/0.3 | 68 (d) |
| **3h** | $CH_2CO_2Et$ | 37 | 58/0.3 | 68 (d) |
| **3i** | $C_6H_5$[f] | 42 | 62/0.3 | 68 (d) |
| **3j** | $CH_2C_6H_5$ | 61 | 64/0.3 | 69 (d) |

[a] Reaction conditions: heated to 170 °C for 1–2 h; during which time the low boiling compounds **3a–e** distill out, while the higher boiling compounds **3f–j** can be extracted out of the reaction mixture. Satisfactory analytical data were obtained for all new compounds listed in this table, with the exception of **3h**, which was contaminated with diethyl succinate. [b] Isolated yields for **3a** and **3j**; in all other cases yields determined by GC. [c] ppm downfield from $CFCl_3$; $J_{HF}$ = 9 Hz, for all cases. [d] Compound previously reported: Renaud, R. N.; Champagne, P. J. *Can. J. Chem.* **1975**, *53*, 529. Compound **3a** was made in 9% yield and reported without supporting spectral data. [e] Compound previously reported: Holland, G. W.; Jernow, J. L.; Rosen, P. U.S. Patent 4 187 381, 1980. Compound **3d** was prepared from the malonic acid half ester and sulfur tetrafluoride in 44% yield. [f] Middleton et al. (Middleton, W. J.; Bingham, E. M. *J. Fluorine Chem.* **1983**, *22*, 574) report fluorine spectral data for the free acid of compound **3i** matching the value given here for the ethyl ester.

can then be transformed to the desired trifluoromethylated compound by loss of one ester and conversion of the $CF_2Br$ to $CF_3$. The overall process is thus the equivalent of allowing a $CF_3^+$ to react with the enolate anion of an ester. In particular, this route permits the attachment of a trifluoromethyl group to an aliphatic carbon, generally a more formidable task than bonding a $CF_3$ to an aromatic nucleus.

## Results

Results for the first step (given in Table I) can be broken down into three distinct groups: (1) Alkyl-substituted malonates **2a–e** give isolated yields of 66–76% simply by allowing the components to stir overnight. (2) Malonates **2f,h–j** having an R group containing functionality or aromaticity give high yields only after extended reaction times of 8–12 days at room temperature. (3) Tricarboxylate **2g**, acetamidomalonate **2k**, and β-keto esters **2l** and **2m** give low yields of the bromodifluoromethyl product even after longer reaction times, minimizing the synthetic potential of these four cases. The transformation to α-trifluoromethyl compounds was not attempted for these four bromodifluoromethyl esters. All products are colorless liquids and have a distinct singlet in $^{19}F$ NMR at approximately 50 δ.

Results for the transformation of (bromodifluoromethyl)malonates to α-trifluoromethyl esters are given in Table II. These do not necessarily represent optimal yields. It is apparent though, that water needs to be excluded and elevated temperatures are required to dissolve a sufficient amount of fluoride ion to allow the reaction to proceed. The products show a doublet in the $^{19}F$ NMR at approximately 70 δ, with a coupling constant of $J_{HF}$ = 9 Hz. $^1H$ NMR shows a distinctive multiplet corresponding to the newly acquired α-proton at approximately 3 δ, and in some cases this appears to be an overlapping doublet of quintets. The boiling points are in the same range as the analogous nonfluorinated α-methyl esters.

No differences in reactivity in the nine (bromodifluoromethyl)malonates can be noticed, indicating little, if any, effect of substitution on this process. However, major differences in the boiling points of the products make it necessary to use two isolation procedures, dependent upon whether the product is higher or lower boiling than the $Me_2SO$ solvent (bp 189 °C). Low boiling materials, Table II, **3a–e**, simply are allowed to distill from the reaction mixture along with dimethyl sulfide and acetaldehyde. These byproducts could be removed later by another distillation. An ether/water extraction of the $Me_2SO$ solution leads to the isolation of the higher boiling compounds **3f,h–j**.

The isolation procedure yields material with purity in the range of 70% to 90%. Three impurities can be detected by spectral and chromatographic methods: a simple ester of the form $RCH_2CO_2Et$ and two α,β-unsaturated esters $CF_2{=}C(R)CO_2Et$ and $HCF{=}C(R)CO_2Et$. No attempt was made to isolate these, as they were present in very small amounts. The fluorine free ester arises from hydrolysis of the $CF_2Br$ unit, due to traces of water in the system or introduced in the workup. (See Discussion.)

Distillation only marginally improves sample purity, however HPLC or a chemical cleanup process can be used. Refluxing the reaction mixture in bromine/methanol followed by distillation substantially decreases the amounts of α,β-unsaturated esters (presumably by bromination of the double bond) and $RCH_2CO_2Et$. It appears the simple ester is also transesterified under these conditions to the lower boiling methyl ester, which can be more easily removed by distillation. The α-trifluoromethyl ester generally remains unaffected, suggesting that the α-$CF_3$ group shields the ester carbonyl, decreasing its susceptibility to attack.

## Discussion

**Step 1.** Although the formation of (bromodifluoromethyl)malonates **2** appears to be a routine alkylation resulting from direct displacement of bromide from dibromodifluoromethane, the actual pathway consists of an ionic chain mechanism involving difluorocarbene, as shown by Wakselman and co-workers.[12-14] They prepared three (bromodifluoromethyl)malonates by this method (**2a**, **2b**, and **2i**).[13] By the use of a 5% excess of NaH, rapid addition of $CF_2Br_2$ at room temperature, and longer reaction times we have improved the yields significantly and have expanded the scope of the reaction as shown in Table I.

Small amounts of brominated and difluoromethylated malonates can be detected by $^1H$ and $^{19}F$ NMR and GC analysis as contaminants of the major product, bromodifluoromethyl-substituted malonates. The presence of these impurities can be accounted for by the ionic chain mechanism. These byproducts are more significant when sodium metal is used to form the malonate carbanions. The use of sodium hydride and the modified conditions described in this paper maximize the formation of (bromodifluoromethyl)malonic esters.

Our work, along with that of Wakselman,[13] shows a relationship between the $pK_a$ of a compound and the reactivity of its conjugate base with $CF_2Br_2$. Acetylides ($pK_a$ ~25) react rapidly with $CF_2Br_2$ and conditions must be controlled to minimize the extent of bromination. Less reactive species tend to give less of the brominated side product. Malonate carbanions ($pK_a$ ~13) react at various rates dependent on the nature of the substituent already attached to the α-carbon. Electron donors destabilize the

(12) Bey, P.; Vevert, J. P.; Van Dorsselaer, V.; Kolb, M. *J. Org. Chem.* **1979**, *44*, 2732.
(13) Rico, I.; Cantacuzene, D.; Wakselman, C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1063.
(14) Rico, I.; Cantacuzene, D.; Wakselman, C. *J. Org. Chem.* **1983**, *48*, 1979.

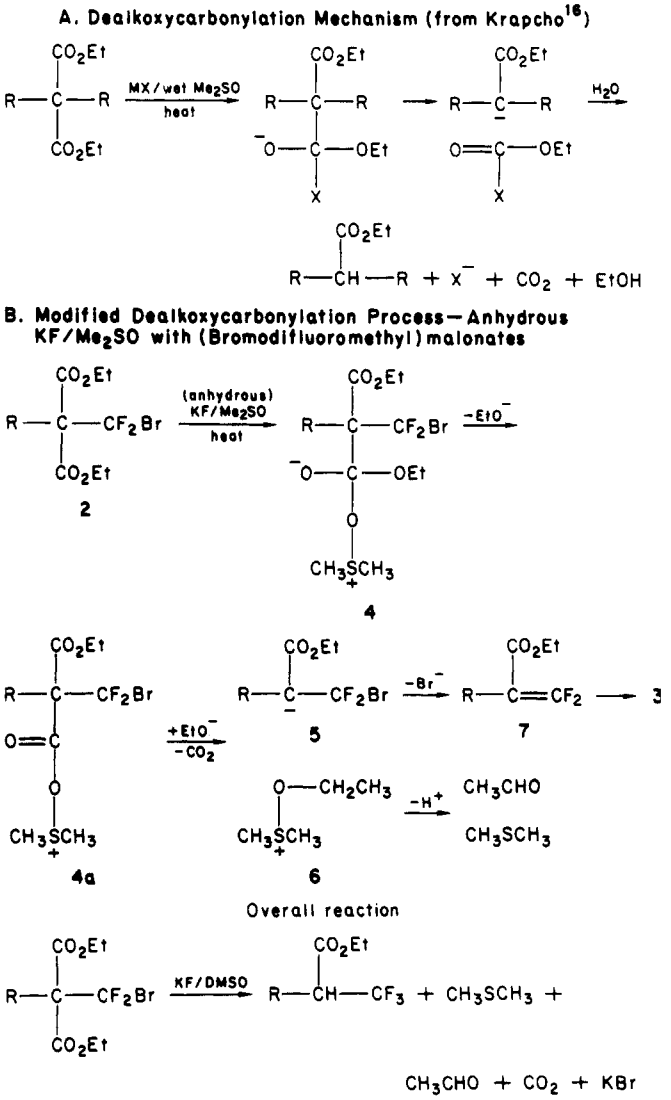
carbanion, increasing its nucleophilicity and rate of reaction; electron acceptors promote the formation of the carbanion and stabilize it, while decreasing its nucleophilicity and reactivity. Both the tricarboxylate **2g** and the acetamidomalonate **2k** contain a $\delta^+$ component $\alpha$ to the carbanion for stabilization by electrostatic interaction or resonance. The low yields in these cases are due to substantially reduced reaction rates rather than a deviation from the expected pathway, as a majority of the starting material is recovered. Conjugate bases of $\beta$-keto esters ($pK_a \sim 11$) and $\beta$-diketones ($pK_a \sim 9$) suffer similar decreased reaction rates with $CF_2Br_2$ due to an increased stability of the anion. An additional complication stems from the ambident nature of the intermediate and is manifest as O-alkylation. Evidence of O-alkylated products in both $\beta$-keto ester cases can be seen in the $^{19}F$ NMR,[15] but the amounts are small with respect to **2l** and **2m**. Wakselman[13] obtained O-alkylated products in low yields when using $\beta$-diketones, but attempts to prepare C-alkylated products were unsuccessful.

**Step 2.** In malonic ester synthesis the normal sequence involves alkylation followed by acid or base hydrolysis to convert the geminal diester to a monoacid through deesterification and decarboxylation. With the bromodifluoromethyl-substituted compounds these conditions result in complete removal of the fluorinated unit, giving $RCH_2CO_2H$. This occurrence indicates the need to maintain anhydrous reaction conditions in order to prevent hydrolysis of the fluorine incorporated in the first step.

The second step, involving transformation of (bromodifluoromethyl)malonates to $\alpha$-trifluoromethyl esters, was accomplished utilizing observations made by Krapcho[16] on dealkoxycarbonylation of geminal diesters. Alkali salts in wet dimethyl sulfoxide can effect the cleavage of one ester from diethyl malonates. The role of the salt was found to be catalytic in nature and the reaction is pictured as proceeding through a carbanion intermediate. We anticipated that, in the case of the (bromodifluoromethyl)-malonates, the dealkoxycarbonylation would proceed together with $\beta$-elimination of bromide ion.[17] This would lead to an $\alpha,\beta$-unsaturated intermediate, a very reactive Michael acceptor, so that when KF is used as the salt, the $CF_3$ group would be formed through nucleophilic attack by fluoride ion (Scheme I).

The mechanism for conversion of (bromodifluoromethyl)malonates to $\alpha$-trifluoromethyl esters only partially follows Krapcho's dealkoxycarbonylation process, which involves small amounts of water (Scheme I, Part A). Under anhydrous conditions the mechanism shown in Scheme I, Part B is proposed. This is supported by the isolation of the primary intermediate (the $\alpha,\beta$-unsaturated, fluorinated ester, **7**) in addition to dimethyl sulfide and acetaldehyde byproducts. Nucleophilic attack at the carbonyl carbon of the ester gives intermediate **4** which then decomposes to **4a**. This loses $CO_2$ to give carbanion **5** and an alkoxy sulfonium ion **6**. The carbanion **5** then eliminates bromide ion to give the unsaturated compound **7**, while the alkoxy sulfonium ion gives rise to dimethyl sulfide and acetaldehyde. The intermediacy of **7** also explains the loss of the entire $CF_2Br$ unit under aqueous

Scheme I



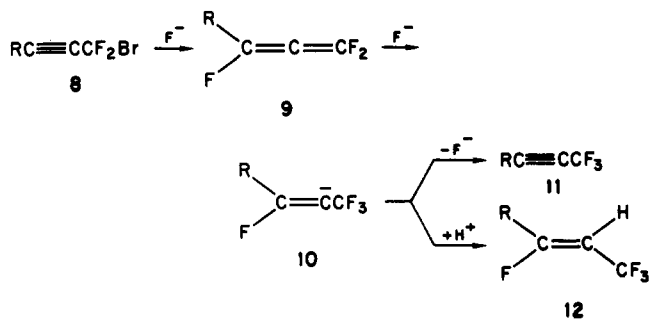

conditions, as the $\alpha,\beta$-unsaturated, fluorinated ester **7** is very susceptible to nucleophilic attack by water, the $CF_2$ group ultimately hydrolyzing to HF and $CO_2$.

The oxidation/reduction process occurring between $Me_2SO$ and the alkoxy moiety of the ester being cleaved probably follows the mechanism established for the Pfitzner–Moffatt[18] method of oxidation of alcohols by $Me_2SO$ in the presence of dicyclohexylcarbodiimide (DCC). Most $Me_2SO$ oxidations involve the same dimethyl alkoxy sulfonium intermediate, $[(CH_3)_2SOR]^+$, **6**.[19]

The conversion of the $CF_2Br$ group to a $CF_3$ is only possible after cleavage of one ester. The direct $S_N2$ displacement of bromide ion by fluoride ion is prevented by electronic and steric factors. Numerous examples can be cited to show that the conversion, $RCF_2X \rightarrow RCF_3$ (where X = Cl, Br), requires internal assistance to displace the halogen before introduction of the third fluorine can occur. (1) Unshared electron pairs on sulfur aid in the displacement of $Br^-$ when bromodifluoromethyl sulfides are converted to trifluoromethyl sulfides using various sources of fluoride ion.[20] (2) 2-Chloro-2,2-difluoroethyl ketones have been transformed to 2,2,2-trifluoroethyl ketones by use of KF in the presence of triethylbenzylammonium chloride.[21]

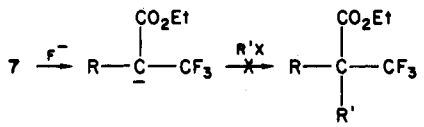
(15) The fluorine chemical shift for **2l** is 50 $\delta$ vs. that of the O-alkylated product at 17 $\delta$. For the six-member ring values of 50 $\delta$ and 14 $\delta$ are seen.
(16) (a) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957. (b) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E. Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138. (c) Krapcho, A. P. *Synthesis* **1982**, 805 and 893.
(17) Two examples of dealkoxycarbonylations with $\beta$-elimination are given in the review by Krapcho, ref 16c. Both involve the loss of trimethylamine in addition to the ester which is cleaved.
(18) Fenselau, A. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 1762.
(19) Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 247.
(20) Suda, M.; Hino, C. *Tetrahedron Lett.* **1981**, *22*, 1997.
(21) Wakselman, C.; Tordeux, M. *J. Fluorine Chem.* **1982**, *21*, 99.

Scheme II

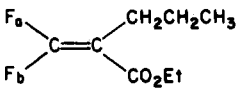


An intermediate of the form $RCOCH{=}CF_2$ is probably involved.[22] (3) In addition to the malonic ester conversions reported here, we have also studied a similar transformation from (bromodifluoromethyl)acetylenes (Scheme II). Most plausible is an $S_N2'$ mechanism, with $F^-$ attacking the acetylenic carbon β to the $CF_2Br$ group, leading to the allene intermediate **9**. Another $F^-$ adds to the terminal $CF_2$ to give **10**, which can regenerate the triple bond or be protonated to give the olefin **12**. When using KF/18-Crown-6 the (trifluoromethyl)acetylene, **11**, is the exclusive product, but with tetrabutylammonium fluoride considerable olefinic product **12** is also obtained.

Three variations of the $KF/Me_2SO$ reaction with **2** have provided us with a better understanding of the mechanism. Dealkoxycarbonylations have been reported to proceed without use of a salt in some cases,[23] therefore we heated **2c** in $Me_2SO$ alone. This led to a small amount of the unsaturated ester and the reaction was much slower. This result does indicate however, that $Me_2SO$ can directly induce the loss of an ester functionality. Since it is possible to alkylate the α-carbanion in dealkoxycarbonylations of simple substituted malonates,[24] an attempt to effect a similar dual transformation in the case of **2c** was made by using benzyl bromide in conjunction with the $KF/Me_2SO$.



No benzylated trifluoromethyl ester was obtained as the $Me_2SO$ oxidizes benzyl bromide to benzaldehyde and benzoic acid prior to alkylation. By using KBr rather than KF in the $Me_2SO$ reaction with **2c**, we were able to isolate a 36% yield of the α,β-unsaturated ester **13**.



**13**

Only a few studies of this type of fluorinated acrylate have been reported in the literature.[25] Although postulated as an intermediate in several reports,[22,26] compounds of the type $CF_2{=}C(R)COR'$ are difficult to isolate in nonanhydrous or nucleophilic media due to further reactions.

## Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The $^1H$ NMR (90 MHz) and $^{19}F$ NMR (84.67 MHz) were obtained on a Varian EM-390 NMR spectrometer. Chemical shifts are reported in ppm relative to internal $Me_4Si$ for $^1H$ NMR data and external $CFCl_3$ for $^{19}F$ NMR, with $CDCl_3$ as the solvent in both cases. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, GA.

High-pressure liquid chromatography (HPLC) was performed with a Waters Associates (Milford, MA) Model 244 liquid chromatograph using a Model 440 absorbance detector set at 254 nm or Differential Refractometer R401. The efficient separation and isolation of samples for elemental analysis were achieved by using a Waters Associates Bondapak C-18 column, 30 cm × 3.9 mm ID, and 45–70% methanol/water as the mobile phase. Sample purity and area percent composition of reaction mixtures were determined by using a HP 5880A gas chromatograph equipped with a 25-m SP 2100 fused silica capillary column. GC conditions employed were a flow rate of 150 kpa and varying oven temperatures in accordance with the boiling points of the samples.

**Starting Materials.** Sodium hydride (50% oil dispersion) was supplied by Ventron. All the monosubstituted diethyl malonates and the two β-keto esters were commercially available from Aldrich Chemical Co. Tetrabutylammonium fluoride, also from Aldrich, comes as a 1 M solution in THF, <5 wt % water. Dibromodifluoromethane was obtained from Armageddon Chemical Co., Durham, N.C. Anhydrous potassium fluoride from Matheson, Coleman and Bell was further dried under vacuum before use. Solvents were dried prior to use: tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl[27] under $N_2$ and dimethyl sulfoxide ($Me_2SO$) was twice distilled from $CaH_2$.

**General Procedure for Alkylation of Diethyl Malonates with Dibromodifluoromethane.** Sodium hydride (50% oil dispersion, 0.10 mol) was transferred to an anhydrous reaction flask under $N_2$ and washed free of the oil with hexane. Dry THF (100 mL) was added, and then the malonate or β-keto ester (0.095 mol) was pipetted into the NaH/THF suspension at room temperature and stirred 0.5 h. Heat was generated and $H_2$ evolved as the sodium salts of the malonic esters formed. Dibromodifluoromethane ($CF_2Br_2$, bp 24 °C, 0.10 mol) was condensed with a dry ice/acetone coldfinger and collected in a graduated receiver, with the amount either weighed or determined by volume ($d$ = 2.3 g/mL). This was joined to the reaction pot by a U tube type connection which allowed the contents to be poured quickly by inverting the tube. This addition at room temperature produced noticeable heating in some cases and within minutes an obvious change in appearance could be observed as NaBr precipitated from solution. The reaction vessel was then tightly sealed to prevent loss of the low boiling methane component and the reaction mixture stirred for the designated period of time (see Table I).

The reaction was worked up by evaporating the THF and taking up the residue in an ether/water extraction. Separation of the two phases followed by drying and concentration of the organic portion yielded the crude reaction mixture, which after vacuum distillation gave the desired product in 90+% purity (as determined by GC analysis). Additional distillation of this material provided analytically pure compound. Percent yield, boiling point, and $^{19}F$ NMR data are given in Table I.

$^1H$ NMR chemical shifts for compounds **2a–m**: **2a** 1.3 (t, 6 H), 1.8 (s, 3 H), 4.3 (q, 4 H); **2b** 1.1 (t, 3 H), 1.3 (t, 6 H), 2.3 (q, 2 H), 4.3 (q, 4 H); **2c** 1.0 (t, 3 H), 1.3 (t, 6 H and m, 2 H), 2.2 (t, 2 H), 4.3 (q, 4 H); **2d** 1.0 (t, 3 H), 1.3 (t, 6 H and m, 4 H), 2.2 (t, 2 H), 4.3 (q, 4 H); **2e** 1.3 (t, 6 H), 3.0 (d, 2 H), 4.3 (q, 4 H), 5.2 (t, 2 H), 5.9 (m, 1 H); **2f** 1.3 (t, 6 H), 2.6 (s, 4 H),[28] 4.3 (q, 4 H); **2g** 1.3 (t, 9 H), 4.3 (q, 6 H); **2h** 1.3 (t, 9 H), 3.2 (s, 2 H), 4.2 (q, 2 H), 4.3 (q, 4 H); **2i** 1.3 (t, 6 H), 4.4 (q, 4 H), 7.4 (s, 5 H); **2j** 1.2 (t, 6 H),

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(28) The two methylenes in the cyanoethyl R group of this compound are magnetically equivalent.

3.6 (s, 2 H), 4.2 (q, 4 H), 7.3 (s, 5 H); **2k** 1.3 (t, 6 H), 2.1 (s, 3 H), 4.3 (q, 4 H), 6.8 (s, 1 H); **2l** 1.3 (t, 3 H), 2.0–2.7 (m, 6 H), 4.3 (q, 2 H); **2m** 1.3 (t, 3 H), 1.7–2.1 (m, 5 H), 2.5 (m, 2 H), 2.8 (m, 1 H), 4.3 (q, 2 H).

**Reaction of (Bromodifluoromethyl)phenylacetylene with KF/18-Crown-6.** (Bromodifluoromethyl)phenylacetylene 8 (R = phenyl) was prepared according to the procedure given by Wakselman.[13] 18-Crown-6 (1.1 g, 0.004 mol) was dissolved in 10 mL of benzene then KF (0.9 g, 0.016 mol) and the acetylene 8 (1.8 g, 0.008 mol) were added. The heterogeneous mixture was refluxed for two days and darkened considerably. After washing and concentrating the organic material, 1.1 g of a mixture of starting material and (trifluoromethyl)phenylacetylene **11** was obtained, in a 7 to 1 ratio determined by GC and $^{19}F$ NMR. Characteristic $^{19}F$ NMR chemical shifts: starting material 32 $\delta$ (s, $CF_2Br$) (lit.[13] 43 $\delta$); product **11** 50 $\delta$ (s, $CF_3$) (lit.[29] 56.4 $\delta$). **11** was not isolated; it is apparent that additional refluxing would be required for sufficient product formation and that fluoride ion is not adequately solubilized in this situation.[30]

**Reaction of (Bromodifluoromethyl)phenylacetylene with Tetrabutylammonium Fluoride.** The acetylene 8 (1.3 g, 0.0056 mol) was added to 10 mL of a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF[31] and stirred. The reaction mixture immediately darkened and was stirred at room temperature for two days with the progress of the reaction monitored by $^{19}F$ NMR. The solvent was then evaporated and the residue taken up in ether and washed with water. Distillation of the dried organic phase yielded 0.43 g of a mixture of four compounds. From GC analysis the mixture was determined to be 65% (*Z*) $C_6H_5CF{=}CHCF_3$, 20% $C_6H_5C{\equiv}CCF_3$, 10% starting material, and 5% (*E*) $C_6H_5CF{=}CHCF_3$. Of these only the major product was chromatographically separated and purified.

(*Z*)-1,3,3,3-Tetrafluoro-1-phenylpropene (**12**): 25% yield calculated by GC; bp 50 °C (5 mm); $^1H$ NMR $\delta$ 5.6 (d of q, 1 H), 7.5 (m, 5 H); $^{19}F$ NMR $\delta$ 58 (d of d, 3 F), 103 (d of q, 1 F); coupling constants $^3J_{HF}$ = 33 Hz, $^3J_{HCF_3}$ = 8 Hz, $^4J_{FF}$ = 16 Hz. Assignment as the *Z* isomer was made by comparison of chemical shifts and coupling constants found in the literature.[32] Anal. Calcd for $C_9H_6F_4$: C, 56.85; H, 3.18; F, 39.97. Found: C, 56.82; H, 3.21; F, 39.85.

**General Procedure for Preparation of $\alpha$-Trifluoromethyl Esters from (Bromodifluoromethyl)malonates.** Product **2** (0.02 mol) from the previous step was dissolved in dry $Me_2SO$ (30 mL) in a three-neck round-bottom flask fitted with a short path distilling unit and thermometer. A two-fold excess of KF (0.04 mol) was added and heating of the heterogeneous mixture was commenced with stirring. In all, three thermometers were used to monitor the reaction and insure the desired rate and extent of heating. Temperatures of the oil bath, $Me_2SO$ solution, and distilling vapors were followed. The $Me_2SO$ solution was quickly heated to 150 °C in the first 0.5 h and then maintained at approximately 170 °C for 1–1.5 h during which time gas evolved, distillate was collected, and the $Me_2SO$ solution developed a dark color.

Isolation of the desired product **3** was dependent on the boiling point of the compound relative to that of $Me_2SO$. Products with boiling points lower than that of $Me_2SO$ were easily collected as they distilled from the reaction; no attempt was made to obtain any other material from the $Me_2SO$ solution. Products with boiling points higher than that of $Me_2SO$ were extracted out of solution with ether after the $Me_2SO$ solution was diluted with a large volume of water. In either case material obtained was very crude and subsequent distillation removed low boiling dimethyl sulfide and acetaldehyde, resulting in a product 70–90% pure. Distillation, chromatography, and/or a chemical cleanup process allowed analytically pure material to be obtained. Percent yield, boiling point, and $^{19}F$ NMR data are given in Table II.

$^1H$ NMR chemical shifts for compounds **3a–j**: **3a** 1.3 (t, 3 H), 1.4 (d, 3 H), 3.2 (septet, 1 H), 4.2 (q, 2 H); **3b** 1.0 (t, 3 H), 1.3 (t, 3 H), 1.9 (q, 2 H), 3.0 (d of quintets, 1 H), 4.2 (q, 2 H); **3c** 1.0 (t, 3 H), 1.3 (t, 3 H), 1.3–2.0 (m, 4 H), 3.1 (d of quintets, 1 H), 4.2 (q, 2 H); **3d** 0.9 (t, 3 H), 1.3 (t, 3 H and m, 4 H), 1.8 (m, 2 H), 3.1 (d of quintets, 1 H), 4.2 (q, 2 H); **3e** 1.3 (t, 3 H), 2.6 (m, 2 H), 3.1 (d of quintets, 1 H), 4.2 (q, 2 H), 5.1 (m, 2 H), 5.7 (m, 1 H); **3f** 1.3 (t, 3 H), 2.1–2.6 (m, 4 H), 3.3 (d of quintets, 1 H), 4.3 (q, 2 H); **3h** 1.25 (t, 3 H), 1.3 (t, 3 H), 2.9 (m, 2 H), 3.6 (m, 1 H), 4.2 (q, 2 H), 4.3 (q, 2 H); **3i** 1.2 (t, 3 H), 4.3 (q, 2 H), 4.4 (q, 1 H), 7.4 (s, 5 H); **3j** 1.1 (t, 3 H), 3.1 (m, 2 H), 3.4 (m, 1 H), 4.1 (q, 2 H), 7.2 (s, 5 H).

**Isolation of the Difluoro $\alpha,\beta$-Unsaturated Ester.** Variations of the dealkoxycarbonylation process, using $Me_2SO$ without KF, $KF/Me_2SO$ with benzyl bromide, and $KBr/Me_2SO$, all followed the general procedure given above. The propyl-substituted (bromodifluoromethyl)malonate **2c** was used in all three reactions, which allowed low boiling products to be readily collected. Details of the $KBr/Me_2SO$ case follow.

Ethyl 2-(difluoromethylene)pentanoate (**13**): (Bromodifluoromethyl)malonate **2c** (4.1 g, 0.0125 mol) was added to KBr (1.5 g, 0.0125 mol) in 20 mL of $Me_2SO$ and heated to 175 °C. Distillate was collected for 1 53.92; at which time pressure suddenly built up in the system and the heating source was quickly removed. After redistillation to remove dimethyl sulfide and acetaldehyde, 0.8 g (36% yield) of **13** was obtained: bp 140 °C; $^1H$ NMR $\delta$ 0.9 (t, 3 H), 1.3 (t, 3 H), 1.5 (sextet, 2 H), 2.2 (t of t, 2 H), 4.2 (q, 2 H); $^{19}F$ NMR $\delta$ 71 (t, $^4J_{HF}$ = 2.4 Hz, $F_a$), 76 (t, $^4J_{HF}$ = 2.8 Hz, $F_b$).[33] Anal. Calcd for $C_8H_{12}F_2O_2$: C, 53.92; H, 6.79. Found: C, 53.64; H, 6.82.

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**Registry No.** **1a**, 609-08-5; **1b**, 133-13-1; **1c**, 2163-48-6; **1d**, 133-08-4; **1e**, 2049-80-1; **1f**, 17216-62-5; **1g**, 6279-86-3; **1h**, 7459-46-3; **1i**, 83-13-6; **1j**, 607-81-8; **1k**, 1068-90-2; **1l**, 611-10-9; **1m**, 1655-07-8; **2a**, 82477-46-1; **2b**, 82477-47-2; **2c**, 91523-39-6; **2d**, 90784-35-3; **2e**, 90784-36-4; **2f**, 90805-99-5; **2g**, 91523-40-9; **2h**, 91523-41-0; **2i**, 82477-48-3; **2j**, 90784-37-5; **2k**, 91523-42-1; **2l**, 91523-43-2; **2m**, 91523-44-3; **3a**, 56354-75-7; **3b**, 90784-38-6; **3c**, 91523-45-4; **3d**, 67787-00-2; **3e**, 90784-39-7; **3f**, 90784-40-0; **3h**, 91523-46-5; **3i**, 90784-42-2; **3j**, 65948-15-4; **8** (R = Ph), 82477-43-8; **11**, 772-62-3; (*Z*)-**12**, 91523-47-6; **13**, 91523-49-8; $Br_2CF_2$, 75-61-6; KF, 7789-23-3; $Bu_4N^+F^-$, 429-41-4; (*Z*)-PhCF=$CHCF_3$, 91523-47-6; (*E*)-PhCF=$CHCF_3$, 91523-48-7.

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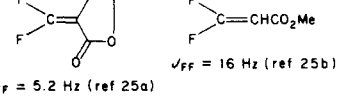
(33) (a) NMR assignments based on study by Moreland, C. G.; Brey, W. S., Jr. *J. Chem. Phys.* **1963**, *39*, 844. (b) The $^{19}F$ NMR spectrum of this compound is interesting as no geminal fluorine–fluorine coupling can be seen. Two singlets appear in the 100 ppm spectrum sweep, showing finer splitting into triplets upon expanding to a 2 ppm sweep width. This is attributed to $^4J_{HF}$ coupling, still with no indication of $^2J_{FF}$ coupling. Lack of geminal fluorine splitting is in contrast to values recorded for similar systems:




$J_{FF}$ = 5.2 Hz (ref 25a) $J_{FF}$ = 16 Hz (ref 25b)

Reference 33a does indicate a wide range of geminal fluorine–fluorine coupling constants are possible in this type of unsaturated system and are highly dependent on the electronegativity of the other substituents.