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PREPARATION OF ESTERS CONTAINING AN α-CF_3 GROUP

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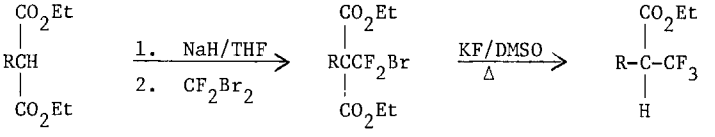
Abstract: Malonates may be converted to esters containing an α-CF_3 group in a two-step process involving bromodifluoromethylation of the malonates followed by decarboxyalkylation-fluorination with fluoride ion in DMSO.

Organic molecules containing the CF_3 group have found wide application.[1] Even so there are relatively few methods available for constructing the CF_3 moiety.[2] These facts led us to consider possible new synthetic schemes involving the combination of nucleophilic carbon with a CF_3^+ equivalent. We wish to report a convenient and practical two-step method for preparing α-trifluoromethyl esters, structure III. These can also be synthesized from malonic acid half esters using sulfur tetrafluoride,[3] although this requires additional equipment and safety precautions due to the highly reactive fluorinating agent. The method presented here avoids use of such reagents, is easily run in conventional laboratory glassware, and gives yields comparable to the single SF_4 case reported.[3] An alternative route employing silyl ketene acetals[4] prepared from, β,β,β-trifluoropropionate has been used to produce a complementary series of trifluoromethyl esters, but attachment of the R group is dependent upon interaction of the ketene acetal with strong electrophilic species.

Monosubstituted diethyl malonates can be transformed to the desired fluorinated esters by modifying the familiar pathway of malonic ester synthesis:



I II III

The first of this two-step process entails treatment of malonic esters (I) with base and then with CF_2Br_2 to obtain the bromodifluoromethyl derivatives II, a procedure patterned after that described by Rico, Cantacuzene and Wakselman.[5] A study of this formal haloalkylation and similar reactions led these investigators to propose a polar chain process involving difluorocarbene to account for the transformation.[5]

A clue to accomplishing the remaining step, the conversion of bromide II to the desired trifluoromethyl derivative III, was uncovered when it was observed that hydrolysis of II produced carboxylic acid IV, a result which we rationalize by degradation according to the series.[6]

$$\text{II} \xrightarrow[-CO_2,\ -Br^-]{\text{ester hydrolysis}} \underset{\text{V}}{RC(CO_2Et) = CF_2} \xrightarrow[-F^-,\ -CO_2,\ -EtOH]{OH^-,\ H_2O} RCH_2CO_2^- \longrightarrow \underset{\text{IV}}{RCH_2CO_2H}$$

Speculating that if intermediate V, an acrylate and a reactive Michael acceptor,[7] could be captured by fluoride in the absence of water (and hydroxide ion), a trifluoromethyl derivative would emerge, we subjected II to potassium fluoride in dimethylsulfoxide. This procedure was devised based on a report by Krapcho and Lovey who found that chloride ion in DMSO effects decarboxyalkylation of malonates in high yield.[8] In our case the fluoride ion obligingly promoted decarboxyalkylation,[9] elimination of bromide and then added to V to generate the α-trifluoromethyl esters III described in Table 1.

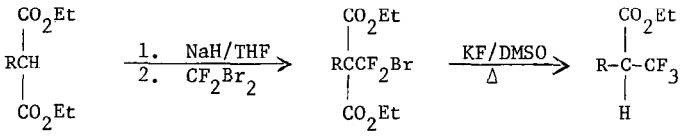
$$\text{II} \xrightarrow[DMSO]{KF} [R\text{-}\underset{\displaystyle CO_2Et}{\underset{|}{\underline{C}}}\text{-}CF_2Br] \longrightarrow [V] \longrightarrow \text{III}$$

The overall result thus furnishes a convenient method for introduction of a CF_3 group into the α-position of esters.

General Procedure: Sodium hydride (50% oil dispersion, 0.10 Mol) was transferred to the reaction flask under N_2 and washed free of oil using hexane. Dry THF was added, followed by malonate (compound I, 0.10 Mol) and the resulting mixture was stirred one half hour. Dibromodifluoromethane (0.10 Mol) was condensed (Dry Ice-acetone) into a graduated receiver, which was then joined to the reaction flask by a U-tube connection. This allowed the CF_2Br_2 contents to be transferred quickly to the reaction flask by inverting the tube. After the addition of the CF_2Br_2, the reaction vessel was tightly sealed to prevent loss of the low boiling methane component and the mixture was stirred at room temperature for the designated period of time (Table 1).

The THF was removed by rotary evaporation and the residue was treated with water and ether. The ether layer was separated, dried, and distilled to yield II. Bromodifluoromethyl derivative II (0.02 Mol) was then dissolved in dry DMSO (30 ml) in a three-neck flask fitted with a short path distillation apparatus. KF (0.04 Mol) was added and the mixture was stirred and heated to 170°C for two hours. During this time the products distilled from the reaction mixture. In those cases where distillation from the reaction mixture was not practical, the solution was diluted with water. The product was isolated after extraction with ether, followed by distillation under reduced pressure (Table 1).

Table 1



I II III

	Compound II[b]				Compound III[b]		
R =	% yield	∿reaction time	bp °C(mmHg)	^{19}F-NMR[a], δ	% yield	bp °C(mmHg)	^{19}F-NMR[a], δ
Me	76	overnight	66 (0.2)	50 (s)	44	112	71 (d)
Et	73	overnight	90 (0.3)	47 (s)	44	128	69 (d)
nBu	66	overnight	95 (0.3)	47 (s)	34	163	69 (d)
CH_2=$CHCH_2$	68	overnight	80 (0.2)	47 (s)	44	143	69 (d)
$NCCH_2CH_2$	80	10 days	118 (0.3)	48 (s)	35	60 (0.3)	68 (d)
$C_6H_5CH_2$	75	10 days	122 (0.3)	47 (s)	61	64 (0.3)	69 (d)
C_6H_5	85	10 days	124 (0.3)	47 (s)	42	62 (0.3)	68 (d)

[a] ppm downfield from $FCCl_3$

s, singlet, d, doublet

J_{HF} = 9 Hz in all cases in III

[b] all new compounds characterized by elemental analyses and spectral methods

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6. The conversion of V to IV is analogous to the hydrolysis of $C_6H_5-\underset{\displaystyle CF_3}{\overset{|}{C}} = CF_2$ to $C_6H_5CH = CF_2$ observed by Klabunde and Burton. Professor D. J. Burton, private communication. Compare also the basic hydrolysis of $CH_3\underset{\displaystyle CF_3}{\overset{|}{C}}HCO_2H$ to $CH_3CH_2CO_2H$ observed by Buxton, M. W.; Stacey, M; Tatlow, J. C. *J. Chem. Soc.* 1954, 366.
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9. The fluoride ion promoted decarboxyalkylation shown is accompanied by formation of acetaldehyde and dimethyl sulfide. The mechanism of this step will be discussed in the full paper.

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