Convenient Preparation of Dimethyl (Trifluoromethyl)malonate and Related Compounds

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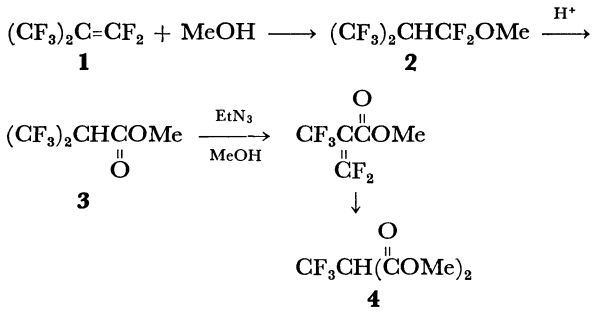
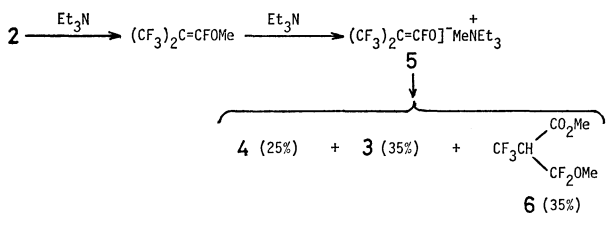
The preparative method for dimethyl (trifluoromethyl)malonate (**4**) from the adduct of perfluoro-2-methylpropene with methanol was improved, and several reactions of this base-sensitive substance were investigated. Alkylation of **4** was achieved by using CsF as a condensing agent, and the Michael addition on vinyl ketones proceeded in triethylamine–pyridine medium.

Organic molecules bearing a trifluoromethyl group have recently been drawing attention because of their possible biological activities.[1,2] One of the attractive methods for the preparation of this kind of compounds is to prepare some versatile intermediates carrying a trifluoromethyl group and to utilize them as building blocks. As one of these building blocks, (trifluoromethyl)malonic ester seemed to be useful because it would afford various trifluoromethylated aliphatic or heterocyclic compounds by the usual synthetic methods.

Dimethyl (trifluoromethyl)malonate (**4**) has already been prepared by Knunyants' group[3,4] from *F*-2-methylpropene (**1**), an extremely toxic perfluoroalkene gas. By their method, the adduct (**2**) of **1** with methanol, a stable liquid, was hydrolyzed with concd sulfuric acid, and the resulting ester (**3**) was subjected to alcoholysis in the presence of triethylamine to give **4**.



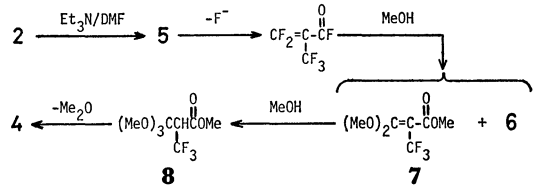
Another report form his group[5] also revealed the formation of **4** together with **3** and **6** from an enolate anion (**5**) generated by the reaction of **2** with triethylamine.



Although the reported yield of **4** is poor, the latter process, a one-step reaction from the adduct **2**, was more attractive to us and we were able to find the optimum conditions to produce **4** in sufficient yields. Some reactions of **4** including alkylations and Michael additions were examined. Although the results were not those which we had expected, we observed several interesting behaviors of **4** in its reaction mode.

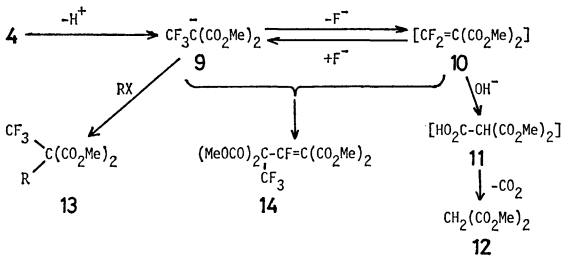
Results and Discussion

Improved Preparation of 4. The adduct **2** was found to be readily converted to the enolate **5** in *N,N*-dimethylformamide by treating it with 2 mol of triethylamine, and **5** thus formed was subjected to methanolysis at room temperature. The major product was a ketene acetal **7**, formed together with a small amount of **6**. By treating the mixture with concd sulfuric acid **4** was obtained in a yield of 68% based on **2**.



Alkylation of 4. Regarding the reactivities of (trifluoromethyl)malonic esters, it is known[4] that they are susceptible to the attack of an alkali, forming a terminal difluoromethylene compound (**10**) which is degraded to the nonfluorinated dimethyl malonate (**12**) *via* a carboxylic acid (**11**). This behavior makes the reaction of **4**, such as alkylation under alkaline conditions, impossible.

To avoid this degradation, cesium fluoride was used as a neutral proton-removing agent. The subsequent alkylation with an alkyl halide gave 2-alkyl-2-(trifluoromethyl)malonic ester (**13**) together with an addition product (**14**) of **9** and **10** as a by-product.



When potassium fluoride instead of cesium fluoride was used in this reaction, the formation of **14** was accelerated considerably. Particularly, in the reaction with benzyl or allyl bromide, the formation of alkylated product **13** was not observed (Table 1). This should be due to the stronger ionizing ability of CsF compared with that of KF. Thus, when CsF was used, the higher concentration of fluoride ions in the reaction

Table 1. Formation of **13** and **14**

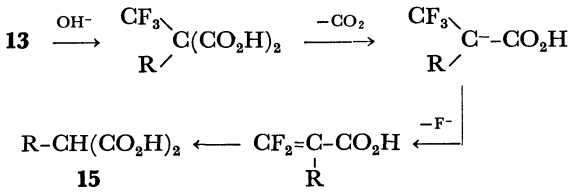
RX	MF Yield/%[a]			
	CsF		KF	
	13	**14**	**13**	**14**
MeI	76	8	51	47
$PhCH_2Br$	22	44	—	82
$CH_2=CHCH_2Br$	19	58	—	90

a) Based on ^{19}F NMR signal intensities.

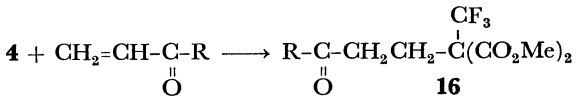
mixture would increase the amount of carbanion **9** rather than **10** in an equilibrium between them, resulting in the increase of the formation of alkylated product **13**. On the other hand, the lower concentration of fluoride ions in the case of KF, would rather favor the formation of the defluorinated intermediate **10** and the subsequent reaction with **9** forming **14** would occur instantly. In the absence of alkyl halides, we could obtain **14** in a good yield by the reaction of **4** with sodium hydride, a much stronger base containing no fluoride ion. A similar compound, tetraethyl ester, had been reported by Knunyants' group.[6]

The alkylation of **4** to give **13** was actually carried out by adding **4** gradually into a mixture of alkyl halide and CsF so that the formation of **14** would be significantly suppressed (Table 2).

Attempted decarboxylation of **13** by heating it with an alkali gave nonfluorinated alkylmalonic acid (**15**), presumably according to the following scheme.



*Michael Addition of **4** to Vinyl Ketones.* As another kind of reactions utilizing the "activated hydrogen" of **4**, its addition to vinyl ketones was carried out. This Michael-type reaction using triethylamine and pyridine as a base and a solvent proceeded smoothly affording 3-oxoalkyl(trifluoromethyl)malonates (**16**) as shown in Table 3.



These derivatives of (trifluoromethyl)malonic esters are expected as useful intermediates for various organic compounds carrying a trifluoromethyl group. Studies for this purpose are now underway.

Experimental[7]

*Dimethyl (Trifluoromethyl)malonate, **4**.* Triethylamine (101.2 g, 1.0 mol) was added dropwise into a mixture of 1,1,3,3,3-pentafluoro-2-(trifluoromethyl)propyl methyl ether (**2**, the adduct of *F*-2-methylpropene with methanol) (116 g, 0.5 mol) and dried *N,N*-dimethylformamide (100 ml), keeping the temperature at 10—20 °C. After the addition, methanol (100 ml) was added dropwise into the mixture over a period of 40 min, during which the temperature was kept below 10 °C by cooling with an ice-bath. After being stirred for 70 min at that temperature, the reaction mixture was poured into water and the resultant oily layer was separated. The aqueous layer was subjected to ether extraction and the ethereal extract was combined with the oil and was dried over $MgSO_4$. After removal of the ether, conc. sulfuric acid (10 ml) was added to the residue and the mixture was stirred overnight at room temperature. After the mixture was poured on ice, the resulting oily material was separated, combined with the ethereal extract from the water layer, dried over $MgSO_4$ and subjected to distillation. (Trifluoromethyl)malonate (67.5 g), bp 65—66 °C/10 mmHg† (lit,[3] 72.5—73 °C/9 mmHg), was obtained in a yield of 68%. ^{19}F NMR: δ −11.1 (d, J_{H-F} 8.0 Hz). ^1H NMR: δ 4.11 (q, $C\underline{H}CF_3$, J_{H-F} 8.0 Hz), 3.83 (s, $C\underline{H}_3$). IR: 1755 (C=O) cm^{-1}.

*Dimethyl Methyl(trifluoromethyl)malonate (**13**, R=Me).* A mixture of dried CsF (9.11 g, 60 mmol), diglyme (41 ml), dimethyl (trifluoromethyl)malonate (4 g, 20 mmol), and methyl iodide (3.12 g, 22 mmol) was stirred overnight at room temperature. The reaction mixture was poured into

Table 2. Alkylation of **4** giving **13**, $RC(CF_3)(CO_2Me)_2$

RX	Reaction conditions			Yield of **13** %	Bp θ_b/°C (mmHg)	NMR δ			IR $\tilde{\nu}$(CO) cm^{-1}	Found(%)		Calcd(%)	
	Solvent	Temp °C	Time h			^{19}F[a] CF_3	^1H $CO_2\underline{Me}$	^1H R		C	H	C	H
MeI	Diglyme	r.t.	12	60	63—65(10)	−7.5(s)	3.81(s)	1.66(s, $C\underline{H}_3$)	1750	39.40	4.21	39.26	4.24
$PhCH_2Br$	Diglyme	70—75	2	45	91—94(0.3)	−12.2(s)	3.73(s)	3.50(s, $C\underline{H}_2$) 7.29(s, Ar$\underline{H}$)	1745	53.58	4.49	53.80	4.51
$CH_2=CHCH_2Br$	Diglyme	70—75	2	47	90—94(9)	−10.6(s)	3.79(s)	2.85(d, $C\underline{H}_2$)	1755	45.19	4.54	45.01	4.62

a) See Ref. 7.

Table 3. Michael addition of **4** to vinyl ketons giving **16**, $RC(O)CH_2CH_2C(CF_3)(CO_2Me)_2$

R in $RC(O)CH=CH_2$	Reaction conditions			Yield of **16** %	Bp θ_b/°C (mmHg)	NMR δ				IR $\tilde{\nu}$/cm^{-1}		Found(%)		Calcd(%)	
	Solvent	Temp °C	Time h			^{19}F(neat)[a] CF_3	^1H (CCl_4) $CO_2\underline{Me}$	Me(R)	$CH_2\underline{CH_2}$	C=O	CO_2Me	C	H	C	H
Me	Pyridine	70	4	74	88—89(0.2)	−10.5(s)	3.82(s)	2.10(s)	2.22—2.69(m)	1720	1745	44.16	4.82	44.45	4.85
Et	Pyridine	70	4	66	89—91(0.2)	−10.7(s)	3.81(s)	1.04(t)	2.23—2.67(m)	1720	1750	46.18	5.36	46.48	5.36

a) See Ref. 7.

† 1 mmHg=133.322 Pa.

water and the resultant oily layer and the ether-extract from aqueous layer were combined and washed with water to remove diglyme. After drying over $MgSO_4$, the ether was evaporated and the residue was subjected to distillation, giving dimethyl methyl(trifluoromethyl)malonate (2.56 g, 60%), bp 63—65 °C/10 mmHg. ^{19}F NMR: δ −7.5 (s, $C\underline{F}_3$). ^1H NMR: δ 3.81 (s, 6H, $CO_2C\underline{H}_3$), 1.66 (s, $C\underline{H}_3$).

*Dimethyl Benzyl(trifluoromethyl)malonate (**13**, R=CH_2Ph).* Into a mixture of dried and powdered CsF (9.11 g, 60 mmol), benzyl bromide (8.55 g, 50 mmol), and diglyme (16 ml), a solution of dimethyl (trifluoromethyl)malonate (4.0 g) in diglyme (20 ml) was added at 70—75 °C over a period of 70 min. After being stirred for 50 min at that temperature, the reaction mixture was poured into water and worked up as usual. Benzyl(trifluoromethyl)malonate, **13** (R=CH_2Ph) (2.6 g, 45%) was distilled out at 91—94 °C/0.3 mmHg.

*Tetramethyl 2,4,4,4-Tetrafluoro-1-butene-1,1,3,3-tetracarboxylate (**14**).* Into a mixture of sodium hydride (0.36 g, 15 mmol) and *N,N*-dimethylformamide (5 ml), a solution of **4** (2.00 g, 10 mmol) in *N,N*-dimethylformamide (5 ml) was added dropwise with cooling the vessel in an ice-bath. After being stirred for 2 h at room temperature, the reaction mixture was poured into dilute aqueous HCl, and worked up as usual. Distillation under vacuum gave **13** (1.27 g, 70%), bp 122—124 °C/0.3 mmHg. Found: C, 40.74, H, 3.53%. Calcd for $C_8H_{12}O_8F_4$: C, 40.01; H, 3.36%. ^{19}F NMR: δ −15.1 (d, $C\underline{F}_3$), +10.7 (q, =C$\underline{F}$–). ^1H NMR: δ 3.77 (s, $C\underline{H}_3$), 3.87 (s, $C\underline{H}_3$), 3.90 (s, ($COC\underline{H}_3$)). IR: 1665 (C=C), 1750 (C=O) cm^{-1}.

Degradation of Dimethyl Methyl(trifluoromethyl)malonate. Into a methanolic solution of sodium methoxide prepared from sodium (0.46 g, 20 mmol) and dried methanol (10 ml), a solution of **4** (0.87 g) in methanol (4 ml) was added. After 3.5 h of stirring at room temperature, the reaction mixture was poured into dil aqueous HCl and worked up as usual. Removal of the ether gave pure dimethyl methylmalonate (0.39 g, 67%) which was identified by comparing its IR, ^1H NMR, and GLC data with those of an authentic sample.

*Dimethyl 1,1,1-Trifluoro-5-oxo-2,2-hexanedicarboxylate (**16**, R=Me).* A mixture of **4** (4.0 g, 20 mmol), methyl vinyl ketone (1.54 g, 22 mmol), triethylamine (0.30 g, 3 mmol), and pyridine (20 ml) was heated for 4 h at 70 °C. The reaction mixture was poured into water and worked up as usual. The adduct (3.97 g), bp 88—89 °C/0.2 mmHg, was obtained and identified in a similar way.

References

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7) All the ^{19}F NMR chemical shifts throughout this article are givin in δ ppm upfield from external trifluoroacetic acid.