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PREPARATION OF 2-FLUOROMALONIC ESTERS AND RELATED COMPOUNDS FROM HEXAFLUOROPROPENE

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SUMMARY

Dimethyl and diethyl fluoromalonates were prepared from hexafluoropropene by its exhaustive alcoholysis or alternatively its ammonolysis and alcoholysis. Fluoromalonates thus obtained or their alkylated derivatives were condensed with o-phenylenediamine or its substituted derivatives to give a number of 1*H*-3-fluoro-1,5-dibenzodiazepin-2,4(3*H*,5*H*)-diones.

INTRODUCTION

Fluoromalonic esters are versatile intermediates for monofluoro heterocycles which are recently receiving attention from the physiological point of view [1]. A number of methods for the preparation of monofluoromalonic esters have appeared in the literature, which include 1) the condensation of ethyl fluoroacetate and ethyl chloroformate under basic conditions [2], 2) the thermal decomposition of diethyl fluoroxalacetate derived from ethyl fluoroacetate and diethyl oxalate [2], 3) the halogen-exchange reaction of diethyl chloromalonate with KF or KHF_2 at a high temperature [3-5], 4) the fluorination of diethyl malonate with perchloryl fluoride (ClO_3F) [6], and 5) the Michael addition of a methoxide ion to trifluoroacrylic esters [7]. The starting materials or reagents for these methods, however, are either expensive and/or toxic, and the procedures are tedious giving only poor yields. Among them, perchloryl fluoride is

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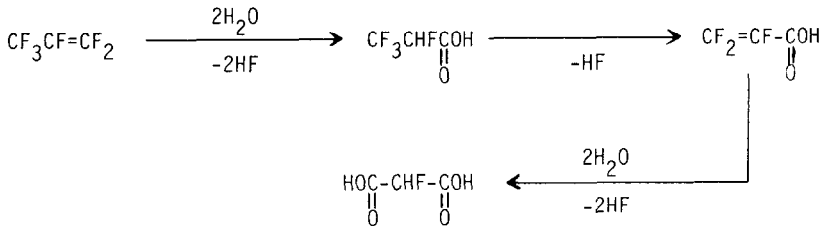
known as a unique fluorinating reagent for active methylene groups, but it always gives a mixture of mono- and di-fluorinated methylene compounds which are difficult to separate.

The fact that a fluorine atom in an organic molecule is a substituent isoelectronic to a hydroxide group suggested us to prepare a fluoromalonic acid by the exhaustive hydrolysis of hexafluoropropene, a commercially available perfluoroalkene with low toxicity.

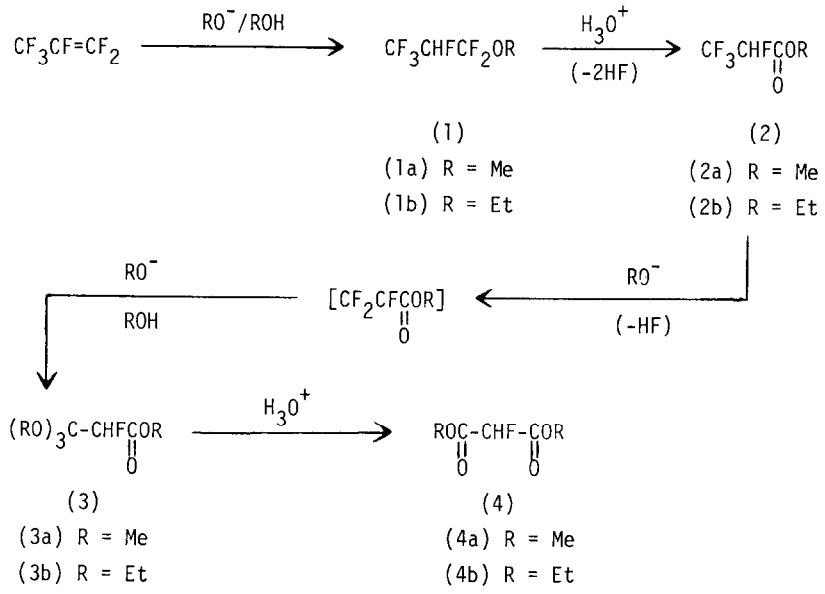


Actually this process has been performed by using an alkoxide ion in an alcohol to give the malonic esters. Alternatively the first step was conducted by ammonolysis to give tetrafluoropropionitrile. Either method afforded the monofluoromalonic ester in a good yield without any danger.

Fluoromalonic esters and their alkylated compounds are useful building blocks for monofluorinated organic molecules, especially fluoroheterocycles. For example, we prepared a number of 1H-3-fluoro-1,5-benzodiazepin-2,4(3*H*, 5*H*)-diones by condensation with *o*-phenylenediamines.

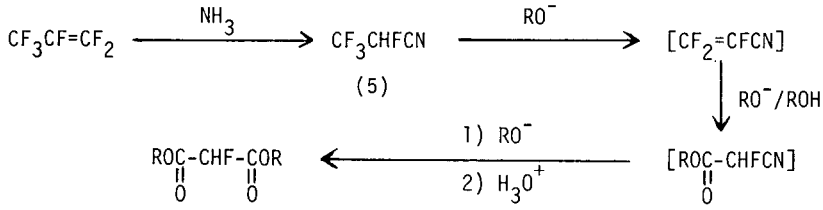
RESULTS AND DISCUSSION

Exhaustive alkoxylation of hexafluoropropene was conducted using a sodium alkoxide in an alcohol. When hexafluoropropene gas was introduced into a solution of a sodium methoxide in methanol at low temperature, hexafluoropropyl methyl ether (1a) was formed quantitatively, which gave methyl 2,3,3,3-tetrafluoropropionate (2a) on treatment with sulfuric acid as was reported by Knunyants and his co-workers [8]. This partially alkoxylated product was subjected to the second alcoholysis. The dehydrofluorination of (2a) followed by the methanolysis of the terminal difluoromethylene group giving the ortho-ester (3a) was carried out using a sodium methoxide in methanol again. The ortho ester was treated with acid and the resultant dimethyl fluoromalonate (4a) was obtained in 50 - 55% yield based on hexafluoropropene.



Diethyl fluoromalonate (4b) was also obtained by using a sodium ethoxide in ethanol in a similar manner (Table 1).

An alternative route to dialkyl fluoromalonates is the way through tetrafluoropropionitrile (5). Ammonolysis of hexafluoropropene giving the nitrile was reported by Knunyants' group [9], who used dioxane as a solvent. We improved the yield of the nitrile considerably by using a large excess of conc. aqueous ammonia in dioxane or tetrahydrofuran, especially in the latter. The nitrile was isolated in ~80% yield, and was converted to a dialkyl fluoromalonate in one pot and in excellent yield (90 - 95%) by dehydrofluorination with an alkoxide, followed by hydrolysis with acid.



(4); (4a) R=Me, (4b) R=Et

TABLE 1

Preparation of 2,3,3,3-tetrafluoropropionates (2) and 2-fluoromalonates (4) by exhaustive alcoholysis of hexafluoropropene

Compd. No.	R	B.p. [Lit] (^{o}C/mmHg)	Yield (%)	IR [CO_2R] (cm^{-1})	NMR ($CDCl_3$) ^{19}F[a] δ ppm (J Hz)	^{1}H δ ppm
(2a)	ME	95-96 [95][b]	74	1780	0, dd (CF_3); 129.0, dq (CHF) (J_{CF_3-F} 9.4; J_{CF_3-H} 5.6; J_{H-F} 39.5)	3.85, s (CH_3) 5.5, dq (CHF)
(2b)	Et	108-109 [108-109][b]	82	1775	0.5, dd (CF_3); 127.5, dq (CHF) (J_{CF_3-F} 11.3; J_{CF_3-H} 6.0; J_{H-F} 44.7)	1.33, t (CH_3); 4.34, q (CH_2) 5.10, dq (CHF)
(4a)	Me	100-102/22 [80-83/13][c]	71	1765	117.0, d (CHF) (J_{H-F} 47.4)	3.90, s (CH_3) 5.23, d (CHF)
(4b)	Et	110-111/22 [82-83/1][c]	63	1770	117.5, d (CHF) (J_{H-F} 46.2)	1.33, t (CH_3); 4.37, q (CH_2) 5.33, d (CHF)

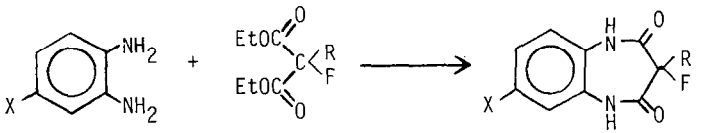
[a] Upfield from ext. CF_3CO_2H. [b] Lit: [8]. [c] Lit: [10].

Comparing the latter process to the former, the first step giving the nitrile (5) required a longer time and larger apparatus, but the second step giving (4) gave a better yield than the second alcoholysis in the former. Thus the former process was suitable for a large scale reaction though the total yield was lower.

The hydrogen atom of the fluoromethylene group in fluoromalonic esters was removed by an alkoxide ion and was replaced by an alkyl group by treating with alkyl halides (Table 2). The reaction was more sluggish than that of a non-substituted malonic ester. This must be attributed to the instability of the carbanion $\bar{C}F(CO_2R)_2$ due to the I_π repulsion between the carbanion and the fluorine atom.

$$\underset{(4)}{CHF(CO_2R)_2} + \underset{R'X = MeI,\ EtBr,\ n\text{-}BuBr}{R'X} \xrightarrow{RO^-/ROH} \underset{(6)\ (6a)\ R = Me\ \ (6b)\ R = Et}{R'\text{-}CF(CO_2R)_2}$$

It is well known that the reaction between o-phenylenediamines and β-dicarbonyl compounds, i.e., β-diketones, β-dialdehydes, β-ketoesters or β-diesters, gives 1,5-benzodiazepine compounds [11]. 2-Fluoromalonic ester could be used as a β-dicarbonyl component in the above reaction and 1*H*-3-fluoro-1,5-benzodiazepin-2,4(3*H*,5*H*)-diones (7) were obtained in good yields (Table 3)



(7) : (7a)～(7g)

Not only 2-fluoromalonic esters but its 2-alkyl derivatives were also used as the component, giving 1*H*-3-fluoro-3-alkyl-1,5-benzodiazepin-2,4(3*H*, 5*H*)-diones. These condensation reactions were carried out by refluxing both components in a sodium ethoxide-ethanol mixture for several hours.

The nitrogen atoms of the 1*H*-3-fluoro-1,5-benzodiazepine derivatives thus obtained could be methylated with methyl iodide giving 1,5-dimethyl derivatives. The biological activity tests for these compounds are now underway.

TABLE 2

Dimethyl (6a) and diethyl 2-R'-2-fluoromalonates (6b)

Compd. No.	R'	B.p. (°C/mmHg) [Lit]	Yield (%)	IR [CO_2R] (cm^{-1})	NMR ^{19}F[CF(R')]^a δppm(J_{vic-HF})	NMR ^1H δppm	Anal (Calcd) C (%)	Anal (Calcd) H (%)
(6a) (nc)	Me	79-80/9	66	1750	78.5 q (J 21.1)	1.72 d (CH_3CF); 3.83 s (OCH_3x2)	44.32 (43.91)	5.61 (5.53)
(6b) (nc)	Me	104-105/23	74	1750	77.8 q (J 20.9)	1.68 d (CH_3CF); 1.35 t (OCH_2CH_3x2); 4.27 q (OCH_2x2)	50.18 (50.00)	6.91 (6.82)
(6a) (nc)	Et	80-82/8	63	1750	90.0 t (J 22.6)	0.99 t (CH_2CH_3); 2.13 dq ($CFCH_2CH_3$); 3.83 s (OCH_3x2)	47.19 (47.02)	6.22 (5.97)
(6b)	Et	125-126/25 [96-99.5/13]^b	79	1750	89.5 t (J 22.2)	0.93 t ($CFCH_2CH_3$); 1.30 t (OCH_2CH_3x2); 2.14 dq ($CFCH_2CH_3$); 4.32 q (OCH_2CH_3x2)		
(6a) (nc)	Bu	98-99/3	72	1755	88.5 t (J 21.6)	0.90 t (CH_3); 1.18-1.50 m (C_2H_4); 1.88-3.43 m (CH_2); 3.83 s (OCH_3x2)	52.60 (52.42)	7.24 (7.33)
(6b)	Bu	133-135/25 [54-55/0.07]^b	85	1750	87.1 t (J 22.2)	0.95 t (CH_3); 1.17-1.55 m (C_2H_4, OCH_2CH_3x2); 2.04 m ($CFCH_2$); 4.23 q (OCH_2x2)		

[a] See Table 1, a . [b] Lit : [10].

TABLE 3

1*H*-3-Fluoro-1,5-dibenzodiazepin-2,4(3*H*,5*H*)-diones (7)

Compd.			M.p.	Yield	IR (cm^{-1})		NMR		Anal (Calcd)		
							^{19}F[a]	^{1}H			
No.	R	X	(°C)	(%)	[CO]	[NH]	δ ppm (J Hz)	δ ppm	C (%)	H (%)	N (%)
(7a)	H	H	>300	60	1680	3200	132.1 d (J 39.5)	5.45 d (CHF); 7.16 s (Ar-H); 10.76 s (NHx2)	56.03	3.65	14.54
(nc)									(55.67)	(3.63)	(14.43)
(7b)	H	Me	>300	70	1670	3260	130.0 d (J 39.5)	2.20 s (CH_3); 5.45 d (CHF); 7.07 s (Ar-H); 10.50 s (NHx2)	57.60	4.59	13.32
(nc)									(57.69)	(4.36)	(13.43)
(7c)	H	Cl	>300	40	1690	3340	129.5 d (J 39.5)	5.44 d (CHF); 7.11 s (Ar-H); 10.30 s (NHx2)	47.03	2.48	11.99
(nc)									(47.20)	(2.64)	(12.25)
(7d)	H	NO_2	262	50	1690	3350	119.5 d (J 39.5)	5.70 d (CHF); 7.40-8.10 m (Ar-H); 10.45 s (NHx2)	44.54	2.53	17.29
(nc)									(45.19)	(2.52)	(17.56)
(7e)	Me	H	245	60	1680	3200	78.0 q (J 20.7)	1.33 d (CH_3); 7.16 s (Ar-H); 10.69 s (NHx2)	57.67	4.57	13.31
(nc)									(57.69)	(4.36)	(13.45)
(7f)	Et	H	283	60	1660	3170	87.5 t (J 19.8)	0.87 t (CH_3); 1.80 dq (CH_2); 7.23 s (Ar-H); 10.98 s (NHx2)	59.34	4.91	12.56
(nc)									(59.46)	(4.99)	(12.61)
(7g)	Bu	H	204	50	1690	3200	85.5 t (J 18.8)	0.66 t (CH_3); 1.60 dt ($CFCH_2$); 1.00-1.30 m (C_2H_4); 7.17 s (Ar-H); 10.90 s (NHx2)	62.15	6.06	11.13
(nc)									(62.38)	(6.04)	(11.19)

[a] See Table 1, [a].

EXPERIMENTAL

Route via tetrafluoropropionate (2a)

Hexafluoropropene gas (255 g, 1.70 mol) was introduced into a solution of sodium methoxide (94 g, 1.74 mol) in methanol (500 ml), cooled in an ice-bath. The gas was completely absorbed in a course of ~3 h. After 1 h of stirring at room temperature, the reaction mixture was poured into water, and the resulting oily layer separated to give a crude product of 1,1,2,3,3,3-hexafluoropropyl methyl ether (1a) (400 ml). The oil was placed in a polyethylene vessel and concentrated sulfuric acid (400 ml) was added dropwise, keeping the temperature below 30 ^{o}C. The mixture was stirred for 1 h at room temperature, thrown into ice water, the the resulting oily layer was separated. After being washed with aq. $NaHCO_3$ solution then with water, it was dried over $MgSO_4$. Distillation gave methyl 2,3,3,3-tetrafluoropropionate (2a) (203 g, 74%), bp 94 - 96 ^{o}C (Lit [8]: bp 95 ^{o}C).

To a solution of sodium methoxide (205 g, 3.8 mol) in methanol (800 ml) the methyl ester (2a) was added dropwise keeping the temperature below 30 ^{o}C. After 30 min of stirring at room temperature, the mixture was made acidic with conc. HCl (250 ml). The resulting suspension was stirred for 1 h at room temperature, filtered, and the filtrate was poured into ice water. The oily material was extracted with ether and the ethereal extract was washed with aq. $NaHCO_3$ solution, then with saturated NaCl solution, and dried over $MgSO_4$. Distillation under reduced pressure gave dimethyl fluoromalonate (4a) (137 g, 71%), bp 111 - 112 ^{o}C/45 mmHg (Lit [10]: bp 80 - 83 ^{o}C/13 mmHg).

In a similar manner using sodium ethoxide in ethanol, ethyl 2,3,3,3-tetrafluoropropionate (2b), bp 108 - 109 ^{o}C (Lit [8]: 108 - 109 ^{o}C) was obtained in 82% yield.

Diethyl fluoromalonate (4b), bp 110 - 111 ^{o}C/20 mmHg (Lit [10]: bp 97 - 97.5 ^{o}C/12 mmHg) was then obtained in 63% yield.

Route via tetrafluoropropionitrile (5)

Aqueous ammonia (25%, 500 g, 7.35 mol) and 1,4-dioxane (200 ml) were put into a 1 l three necked flask fitted with a dry ice-acetone condenser, a thermometer and an inlet gas filter. Hexafluoropropene (291 g, 1.94

mol) was introduced into the solution in a course of 5 h, keeping the temperature at -5 - 0 °C. After 3 h of stirring at this temperature, the oil which had separated was extracted with toluene, washed with water, and dried over $MgSO_4$. Distillation gave 2,3,3,3-tetrafluoropropionitrile (5) (187 g, 76%), bp 40 °C (Lit [9]: bp 40 - 41 °C).

To a solution of sodium methoxide (190 g, 3.5 mol) in methanol (800 ml) the nitrile (5) (127 g, 1.0 mol) was added dropwise keeping the temperature below 10 °C. The reaction mixture was allowed to warm to room temperature and stirred for 30 min, and was then acidified with conc. HCl. After 30 min of stirring at room temperature, the mixture was poured into ice water. The oily product was extracted with diethyl ether, washed with aq. $NaHCO_3$ solution, then with saturated NaCl solution. After drying over $MgSO_4$, distillation under reduced pressure gave dimethyl fluoromalonate (4a) (138 g, 92%), bp 90 - 91 °C/15 mmHg.

Dimethyl n-butylfluoromalonate

Into a solution of sodium (2.3 g, 0.1 mol) in ethanol (100 ml), diethyl fluoromalonate (17.8 g, 0.1 mol) was added dropwise. The mixture was stirred at room temperature for 30 min and n-butyl bromide (14 g, 0.1 mol) was added dropwise and the whole was refluxed for 1 h. The reaction mixture was worked up as usual and distillation under reduced pressure gave diethyl n-butylfluoromalonate (6b, R' = n-Bu) (17.9 g, 84%), bp 133 - 135 °C/25 mmHg (Lit [10]: 54 - 55 °C/0.07 mmHg).

In a similar manner, diethyl methylfluoromalonate (6b, R' = Me), bp 104 - 105 °C/23 mmHg, was obtained in 74% yield.

1*H*-3-Fluoro-1,5-benzodiazepin-2,4(3*H*,5*H*)-dione

To a solution of a sodium ethoxide (0.68 g, 10 mmol) in ethanol (10 ml) were added *o*-phenylenediamine (1.1 g, 10 mmol) and diethyl fluoromalonate (1.8 g, 10 mmol). The resulting suspension was refluxed for 5 h and allowed to stand overnight at room temperature. The reaction mixture was acidified with aq. HCl and the precipitate formed was collected and recrystallized from acetic acid, giving the pure product (1.2 g, 60%), mp > 300 °C.

In a similar manner, *o*-phenylenediamine and diethyl 2-methyl-, 2-ethyl- or 2-butyl-2-fluoromalonate were condensed to give 1*H*-3-alkyl-3-fluoro-1,5-benzodiazepin-2,4(3*H*,5*H*)-diones.

1*H*-3-Fluoro-1,5-dimethyl-1,5-benzodiazepin-2,4(3*H*,5*H*)-dione

To a mixture of 1*H*-3-fluoro-1,5-benzodiazepin-2,4(3*H*,5*H*)-dione (10 mmol) and sodium ethoxide (20 mmol) in ethanol (20 ml), methyl iodide (20 mmol) was added dropwise over 30 min, and refluxed for 3 h. On cooling, the reaction mixture was acidified, and resultant precipitate was collected. Recrystallization from methanol gave colorless needles of the pure product in 55% yield, mp 300 °C.

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