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PREPARATION OF SOME 4- AND 5-FLUOROMETHYLATED 1,3-DIOXANS

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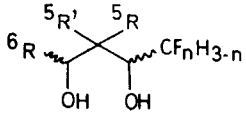
SUMMARY

Difficulties associated with the successful preparation of 4- and 5-fluoromethylated 1,3-dioxans (III) ($^{5'}R = {}^{5}R = H$) and (IV) ($^{5}R = Me$; $^{2}R = H$ or Me) are reported. Claisen condensation between ethyl monofluoroacetate and methyl ketones afforded furan derivatives (e.g. compound (V)).

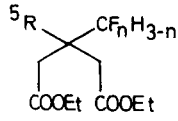
Attempts to dialkylate fluorinated 1,3-diketones by classical procedures did not yield the corresponding 2,2-*gem*-alkylated 1,3-diketones but rather asymmetric ketones by β-diketone degradation, the fluorinated moiety being lost.

INTRODUCTION

1,3-Dioxans, such as (III) and (IV) ($n = 1$–3), may be obtained by acid-catalyzed acetal formation from suitable 1,3-diols, the latter being prepared either by reduction of β-diketones (I) or of the appropriate substituted malonates (II).



I



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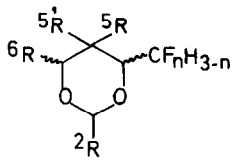
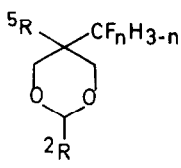


III



IV

Conformational studies on these compounds have been described elsewhere[1–3], together with NMR spectral data[1,2] which included some long-range coupling phenomena[4].

RESULTS AND DISCUSSION

1,3-Diols

Attempted preparation of these compounds from compound (I) encountered difficulties both during the reduction stage and during preparation by Claisen condensation of the appropriate β-diketones.

Thus, reduction conditions were found to be critical for ^6R = Me, especially when $n \neq 2$, not only because of the possibility of extensive defluorination (hydrogenolysis) (*e.g.* for $n = 1$), but also because the intermediate borate esters were found to be extremely stable towards acidic hydrolysis (for $n = 1$ and 3). Reduction with Raney nickel (ethanol at 100°/100 atm) was prevented by the acidic nature of the diketones ($^5R = {}^5'R = H$). Only aluminium chelates of the starting compounds were formed, or alternatively, but only after very long reaction times (several days), reductive cleavage was predominant. For $n = 2$, the procedure described by Dale[5], using sodium borohydride, gave satisfactory results (yields 70% or better), but with $n = 1$ and 3 the borate esters formed were so stable that only prolonged boiling in alkaline solutions (10% sodium hydroxide) could be used. Presumably the degree of polymerization of these borate esters is appreciable. In addition, any time lapse between reduction and work-up appeared to increase their resistance towards eventual decomposition (through polyborate reorganization?). The presence of excess hydride caused extensive defluorination during alkaline work-up, *e.g.* 70% defluorination occurred when ^6R = Me and $n = 1$ in compounds of type (I). Attempts to adjust the basicity during reduction by using partly neutralized[6] hydride solutions were unsuccessful.

The best results were obtained by using an excess of borohydride, followed by destruction of this excess with acetone, before the solution was boiled further. No reductive defluorination was observed under these circumstances and the yield was fairly good ((I); ^6R = Me; $^5R = {}^5'R$ = H; $n = 1$; yield = 60%).

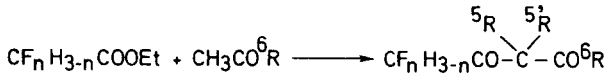
The continuous chloroform extract (the diols are very soluble in water) can be worked up in the usual way. The diols were not isolated as such, but directly ring closed with the appropriate carbonyl compound, affording the 1,3-dioxanic compounds (III).

Compounds of type (IV) could be prepared by reduction with lithium aluminium hydride (LAH) according to classical procedures. However, due to difficulties in the synthesis of the appropriate malonate derivatives (II), this route could only be used for the preparation of (IV) when ^5R = Me and $n = 2$ (see further, 5,5-disubstituted 1,3-dioxans).

β-Diketones (Scheme 1)

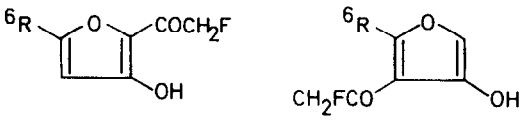
Conditions for the Claisen condensation between the appropriate ethyl fluoroacetate and methyl ketone (^6R = Me or t-Bu) are critical. For $n = 3$ (trifluoroacetate), the general procedure may be followed[7], but for $n = 2$ and

Scheme I



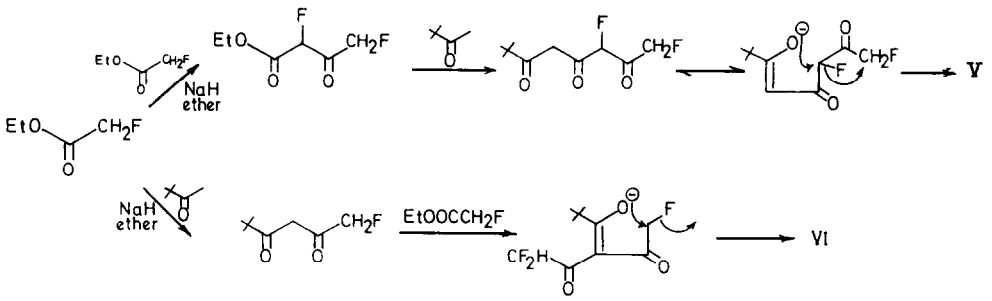
VII

1 yields were very low due to self-condensation of the esters and the ketones (especially when ^6R = Me). Remarkably, self-condensation of monofluoroacetate ($n = 1$) was found to be appreciably greater than for the difluoro derivative ($n = 2$). Nevertheless, only the use of sodium hydride under somewhat modified conditions (see experimental section) gave good results. With ^6R = t-Bu, the sole reaction product was found to be (V) ((VI) is less probable, as follows from the spectral behaviour, see experimental section). This may be formed by multiple condensation reactions as depicted in Scheme 2. Changing the relative proportions of ester and ketone did not result in the desired diketone (^6R = t-Bu) but only influenced the yield of the furan derivative.



V VI

Scheme II



Even with ^6R = Me, formation of the furan derivative ((V); ^6R = Me) was still observed, which, together with aldolization of acetone itself, explains the low yield (20%) of the desired β-diketone. All these side reactions were less pronounced when ethyl difluoroacetate was used, when no furan derivative, for example, could be detected in the reaction mixture. Attempts to prepare the diketone with ^6R = t-Bu and $n = 1$, using boron trifluoride as the catalyst[8], failed, as also did condensation (either in the presence of sodium hydride or boron trifluoride) with ethyl monochloroacetate. Table 1 lists the β-diketones prepared together with some NMR spectral data.

Thorough fractionation of the ether extracts of the β-diketones was found

necessary because of their very high volatilities. In the case of the trifluoro t-butyl derivative, however, fractionation was not attempted, the direct use of the enriched fractions for further reduction being preferred. Yields in Table 1 are based on gas chromatographic sampling.

An attempt to alkylate the diketones ($^5R = {}^{5'}R \neq H$, $n = 3$), using the alkylation method for acetylacetone[9], failed. Dialkylation presumably proceeds very rapidly even in the presence of sodium carbonate in acetone, but diketone degradation cannot be avoided with the result that isopropyl methyl ketone, for example, may be obtained from trifluoroacetylacetone in good yield. The method could perhaps be adopted for the preparation of unsymmetric ketones, but no attempt has been made to extend the scope of the reaction. If, however, trifluoroacetylacetone was treated with sodium hydride in DMF and subsequently with methyl iodide for 20 h at 60°, only the monomethylated derivative (^5R = Me; $^{5'}R$ = H) was formed (100% enol, NMR), although repeated treatment under similar conditions led to diketone degradation.

1,3-Dioxans ((III) and (IV))

Treatment of β-diols (mixtures of *threo* and *erythro*) with paraformaldehyde gave dioxans of type (III) and eventually (IV) (^2R = H), and with paraldehyde gave dioxans of types (III) and (IV) (^2R = Me), all in good yield. The reactions were carried out in benzene using catalytic amounts of toluene *p*-sulfonic acid, followed by azeotropic removal of water and the usual work-up. Table 2 lists some data, together with the kind of phase used for gas chromatographic preparative separation of the different isomers.

Special preparative methods were however necessary for the dioxans of type (IV). Thus, the monofluoro derivative ((IV); $^{5'}R = CFH_2$, ^5R = Me, ^2R = H) was obtained from the corresponding hydroxy derivative[11] ($^{5'}R = CH_2OH$). The conversion developed by Ayer[12] for the replacement of hydroxy groups by fluorine, using *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine, failed because the acetal function was attacked and opened. However, when the hydroxymethyl derivative ((IV); $^{5'}R = CH_2OH$, ^5R = Me, ^2R = H) was transformed to the mesylate and the latter treated with potassium fluoride[13] in diethylene glycol, the desired derivative was obtained.

The difluoromethylated dioxan ((IV); $^{5'}R = CF_2H$, ^5R = Me, ^2R = H) could be obtained by treating diethyl methylmalonate with difluorocarbene, the latter being generated from chlorodifluoromethane according to the method of Sarett *et al.*[14].

Several other carbene precursors were also tried in an attempt to prepare the corresponding t-butyl derivative (starting from diethyl t-butylmalonate) but, however, without success. Despite the fact that the t-butyl group imposes much more severe steric requirements, this failure is unexpected in the light of the low selectivity and the high reactivity of carbenes.

TABLE 1

PREPARATIVE AND NMR DATA FOR $CF_nH_{3-n}COCH_2CO^6R$

n	^6R	B.p. (°C/760 mmHg)	Yield	NMR data [a] δ(Me)	=CH [b]	CF_nH_{3-n}	^2J(H,F)	M^+
3 [g]	Me	110	52	2.19	5.86	–	–	154.08
3 [g]	t-Bu	[c]	[c]					–
2(nc)	Me	133	69	2.16	5.83 [e]	5.78	54.6	136.09
2(nc)	t-Bu	160	71	1.19	5.92	5.8	53.9	178.18
1 [g]	Me	125	20 [d]	2.08	5.79 [e]	4.75	47.3	118.10
1(nc)	t-Bu	–	0 [f]	1.26 [f]	5.89 [f]	5.19 [f]	46.9 [f]	200.20

[a] Shifts in ppm from TMS. Solutions in CCl_4.

[b] All diketones occurred exclusively as the enol form.

[c] Not isolated; the ethereal extract was directly used as such.

[d] Also (V) (^6R = Me) was formed. See text.

[e] An interesting allylic long-range coupling of 3.5 Hz was observed between =CH and ^{19}F for the compound with $n = 1$, but NOT when $n = 2$.

[f] The only product (of which the NMR signals recall very closely a β-diketonic structure) had in fact structure (V), as follows especially from mass spectral data ($M^+ = 200$) and further chemical proof (see experimental section).

[g] This compound has been described in the literature [18].

TABLE 2

PREPARATIVE AND GAS CHROMATOGRAPHIC DATA FOR SEPARATION OF DIFFERENT ISOMERS OF DIOXANS (III) AND (IV) (NEW COMPOUNDS)

n	^{2}R	^{6}R	Yield (%)	B.p. (°C/mmHg)	Gas chromatographic data [c] Phase	Temp.(°C)	Mass (µl)	α [a]	Isomeric composition [b]	M$^+$ [i]
Dioxan (III)										
3	H	Me	≈80	132/760	PTMO	110	200	1.13	1:56% *trans* [d] 2:44% *cis*	152.13
3	H	t-Bu	78	165/760	PTMO	150	800	1.20	1:66% *trans* [a] 2:34% *cis*	194.22
3	Me	Me	≈80	138/760	PTMO	120	200	1.32 1.32	1:26% ^{4}R-*trans*, ^{6}R-*cis* [d] 2:66% ^{4}R-*cis*, ^{6}R-*cis* 3:8% ^{4}R-*cis*, ^{6}R-*trans*	166.15
2	H	Me	84	144/760	PTMO	110	200	1.12	1:65% *cis* 2:35% *trans*	134.14
2	H	t-Bu	90	180/760	QF_1	110	8(!) [e]	1.04	1:44% *trans* 2:56% *cis*	176.33
2	Me	Me	90	148/760	QF_1	130	100 [f]	1.10	1:mixture of ^{4}R-*trans*, ^{6}R-*cis* and ^{4}R-*cis*, ^{6}R-*cis* [f] 2:^{4}R-*cis*, ^{6}R-*trans*	148.16
1	H	Me	75	157/760	PTMO	170	500	1.13	1:58% *cis* 2:42% *trans*	116.14
1	Me	Me	79	164/760	PTMO	180	400	1.11 1.10	1:44% all *cis* 2:34% ^{4}R-*trans*, ^{6}R-*cis* 3:22% ^{4}R-*cis*, ^{6}R-*trans*	130.16
Dioxan (IV)										
n(^{5}'R)	^{2}R	^{5}R								
1	H	Me	>60 [g]	80/16	Carbowax					116.14
2	H	Me	61 [g,h]	GC [j]	QF_1					134.14
2	Me	Me	*ca.* 60 [h]	GC [j]	QF_1	150	100	1.10	1:11% axial CF_2H 2:89% eq. CF_2H	148.16

TABLE 2 *(continued)*

[a] Ratio of (corrected) retention times of two successive peaks.
[b] For structure assignment see ref. 1 and 2. For the acetaldehyde-acetals, the *cis,trans* assignment is with reference to the (equatorial) Me-2.
[c] Length: 20 m, φ 1 cm, Chromosorb W30/60.
[d] In contrast to the other series ($n \neq 3$) and the simple 4,6-dialkyl-1,3-dioxans[10], the order of retention is *trans–cis*.
[e] As in this series the retention order (see footnote d) is changed, separation was only partly successful, using extremely small mass values.
[f] No separation, even with lower mass values, see footnote e. The three components could, however, be separated on capillary columns.
[g] For method of preparation, see text.
[h] Yield after gas chromatographic purification.
[i] High-resolution mass spectrometry.
[j] GC = gas chromatography.

EXPERIMENTAL

The NMR spectra of the dioxanic compounds have already been discussed[1,2].

Preparation of β-diketones (VII)

The method used for the preparation of trifluoroacetylacetone ((VII); ^6R = Me, $n = 3$) and the t-butyl analogue (^6R = t-Bu) employed the classical procedure using sodium hydride[7]. For $n = 2$ (from ethyl difluoroacetate, Pennisular Chem. Res.) or $n = 1$ (from ethyl monofluoroacetate[15]), a slightly different procedure had to be followed. Thus, to a suspension of 0.75 mole (18.0 g) of sodium hydride in 150 ml of ether, was slowly added an ethereal solution (100 ml) containing 0.75 mole of the acetate and 0.75 mole of the appropriate ketone. Addition of ethanol was not used to initiate the reaction but instead the reaction mixture was gently heated. Once reaction started, the reaction mixture was held at 0°. After 12 h, the mixture was poured on to 250 g of crushed ice and 50 g of conc. sulfuric acid.

It proved very difficult (especially when ^6R = t-Bu) to isolate the β-diketone by fractionation from the dried ethereal extract. For (VII) (^6R = Me, $n = 1$), it was necessary to eventually isolate the β-diketone as its copper chelate[16]. The corresponding t-butyl analogue ((VII); ^6R = t-Bu, $n = 1$) could not be obtained. Instead, ethyl-1,3-difluoro-2-oxopropane carboxylate was formed in 40% yield, together with a faintly yellow crystalline product (40%) which could be readily purified by sublimation (140°) and by gas chromatographic methods (QF_1, temp. 190°). Although its NMR spectrum was very similar to that of the expected β-diketone (Table 1), mass spectral analysis indicated that the compound was $C_{10}H_{13}O_3F$ (high resolution; (*m/e, I*): 200 (58), 185 (100), 167 (97)).

The compound resisted any attempt at further hydrogenation ($NaBH_4$, Raney Ni, PtO_2) which indicates the lack of a β-diketone function. From the mass spectroscopic molecular weight, two structures (either (V) or (VI)) are possible. We prefer structure (V) because the absorption maximum at 295 mμ (MeOH) in the UV spectrum shows a pronounced bathochromic shift in an alkaline medium (λ_m = 265 and 327 mμ in MeOH, 0.1 *N* NaOH). This may be best explained by the assumption of a vinyl hydroxyketone structure such as (V).

In addition, the shift value of the vinylic proton in the NMR spectrum (δ = 5.89) has a value which is more probable for a proton of the β-furan type, since an α-furan type proton such as that in (VI) has a shift value which is normally greater than 6.0.

Reduction of β-diketones to 1,3-diols (I)

The procedure according to Dale[5] gave satisfactory results except for trifluoroacetylacetone ((VII); ^6R = Me, $n = 3$) and monofluoroacetylacetone ((VII); ^6R = Me, $n = 1$) for which the following procedure was used. An ice-

cooled methanolic solution of 0.15 mole of the diketone was added to a suspension of 0.15 mole of sodium borohydride in 100 ml methanol which had been stabilized by the addition of 300 mg sodium hydroxide. After 2 h, acetone was slowly added at 0° and the volume reduced to 50 ml. The residue was boiled for some hours with mannitol, continously extracted with chloroform and then worked up in the usual manner. No fluorine hydrogenolysis was observed under these circumstances.

The diols were not usually isolated in the pure state. The evaporated residues gave almost quantitative yields and were used as such for the direct cyclization to the corresponding dioxan.

Transformation of diols to dioxans

The dioxans were obtained by treatment of the dioles under acidic conditions in benzene or toluene with an excess of the appropriate aldehyde followed by continuous removal, by means of a Dean–Stark separator, of the water formed. After the theoretical amount of water had been obtained, the mixture was treated with sodium carbonate, filtered and fractionated. The calculated yields of dioxans based on the amount of β-diketones used (Table 2) are good to excellent.

5'-Fluoromethyl-5-methyl-1,3-dioxan ((IV); $^2R = H$, $^{5'}R = CFH_2$, $^5R = Me$)

5'-Hydroxymethyl-5-methyl-1,3-dioxan (17g) (prepared[17] from methyl tris-(hydroxymethyl)methane [Fluka]) was treated in 200 ml pyridine at 0° with 16.1g mesyl chloride. After 2 h, 250 ml of water was added and the mixture extracted with chloroform. Fractionation afforded 21 g (70% yield) of the mesylate ($^{5'}R = CH_2OMes$) b.p. 185°/16 mmHg. The mesylate (10.5 g) was treated in 100 ml diethylene glycol with a large excess (5.8 g) of *thoroughly* dried sodium fluoride (water removed azeotropically with benzene) at 160°. The pressure was held at 20–30 mmHg and the desired fluoromethyl derivative directly distilled from the reaction mixture (together with some solvent). To the distillate, 100 ml water was added and the dioxan extracted with ether. Fractionation gave 5'-fluoromethyl-5-methyl-1,3-dioxan in good yield (b.p. 80°/16 mmHg). Purification was achieved by the use of preparative gas chromatographic methods using 20% Carbowax on Chromosorb W 30/60.

(2-Methyl)-5'-difluoromethyl-5-methyl-1,3-dioxan ((IV); $^{5'}R = CF_2H$, $^5R = Me$)

Diethyl difluoromethylmethylmalonate[14] was obtained in 76% yield, b.p. 92°/15 mmHg. Similar experiments, starting with diethyl t-butylmalonate were unsuccessful even at increased temperatures. At 200°, the malonate decomposed to ethyl-β,β-dimethylbutyrate. No reaction occurred when sodium difluorochloro-acetate[16] was used as a carbene precursor.

Reduction of the malonate was achieved in quantitative yield by treatment of an ethereal solution with lithium aluminium hydride under reflux. Usual work up gave the white crystalline diol (NMR) which was immediately treated with

paraformaldehyde or paraldehyde in benzene in the presence of catalytic amounts of toluene *p*-sulfonic acid. The corresponding 1,3-dioxans were thus obtained in good yield. They were purified and separated (Table 2) by means of gas chromatography.

ACKNOWLEDGMENTS

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REFERENCES

1 P. DIRINCK AND M. ANTEUNIS, *Canad. J. Chem., 50* (1972) 412.
2 M. ANTHEUNIS AND P. DIRINCK, *Canad. J. Chem., 50* (1972) 423; M. ANTEUNIS AND F. BORREMANS, *ibid.*, in press.
3 P. DIRINCK AND M. ANTEUNIS, *J. Fluorine Chem., 2* (1972) 194.
4 M. ANTEUNIS, R. VAN CAUWENBERGHE AND P. DIRINCK, in preparation.
5 J. DALE, *J. Org. Chem.*, 26 (1961) 910; *cf.* A. HAJOS, *Komplexe hydride*, Deutscher Verlag Wissenschaften, Berlin, 1966; N. G. GAYLORD, *Reduction with Complex Metal Hydrides*, Interscience, New York, 1956.
6 L. FIESER AND M. FIESER, *Reagents for Organic Synthesis*, Wiley-Interscience, New York, 1967, p. 1050.
7 C. R. HAUSER, F. W. SWAMER AND J. T. ADAMS, *Org. Reactions, 8* (1954) 59.
8 J. T. ADAMS AND C. R. HAUSER, *J. Amer. Chem. Soc., 67* (1945) 284.
9 A. W. JOHNSON, E. MARKHAM AND R. PRICE, *Org. Synth., 42* (1962) 75; H. NOZAKI, Z. YAMAGUFI, T. OKADA, R. NOYARI AND K. KAWANISI, *Tetrahedron, 23* (1967) 3993.
10 D. TAVERNIER, *Ph. D. Thesis*, Ghent, 1971.
11 J. DELMAU, *Bull. Soc. Chim. France*, (1965) 1950.
12 D. E. AYER, *Tetrahedron Letters*, (1962) 1065; *cf.* L. H. KNOX, E. VERLARDE, S. BERGER, D. CUADRIELLO AND A. D. CROSS, *Tetrahedron Letters*, (1962) 1249.
13 W. F. TAYLOR AND P. W. KENT, *J. Chem. Soc.*, (1958) 872; F. L. M. PATTISON AND G. E. MILLINGTON, *Canad. J. Chem., 34* (1956) 757.
14 T. Y. SHEN, S. LUCAS AND L. H. SARETT, *Tetrahedron Letters*, (1961) 43; *cf.* J. HINE AND J. J. PORTER, *J. Amer. Chem. Soc., 79* (1957) 5493.
15 HOUBEN-WEYL, *Halogenverbindungen*, Thieme, Stuttgart, Bd. V, Teil 3, 1962, p. 151.
16 A. P. KRAPCHO, *J. Org. Chem., 27* (1962) 2375.
17 M. M. BRUBAKER AND R. A. JACOBSON (to E. I. du Pont de Nemours & Co.), *U.S. Pat., 2,292,926* (1943).
18 K. SATO, H. OCHI AND K. ARAKAWA, *Bull. Chem. Soc. Japan, 42* (1969) 1747.