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An Expedient Stereoselective Access to (Z)-2-Fluoroalkenoates

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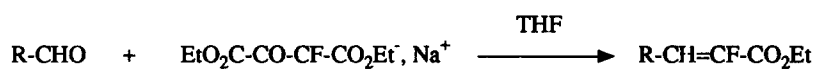
Abstract: *The reaction between an aldehyde R-CHO and diethyl 2-oxo-3-fluorobutan-1,4-dioate as its sodium salt EtO_2C-CO-CF-CO_2Et^-, Na^+ mainly leads in THF to (Z)-2-fluoroalkenoates R-CH=CF-CO_2Et (Z/E≥80/20), the Z-stereoselectivity depending on the bulk of the R group.*

2-Fluoroalkenoates R-CH=CF-CO_2R' **3** are important building blocks in the field of biologically active fluoro-compounds, such as pheromones,[1] retinoids,[2] and stereoselective methods of preparation of these esters are therefore of great interest. The Horner-Wadsworth-Emmons reaction between a phosphonofluoro-acetate and aldehydes appears to be a general route for obtaining mainly the *E*-isomers of **3** (*E*/Z>90/10) in good yields,[3] however, preparation of the corresponding *Z*-isomers is more difficult as can be seen from several more or less sophisticated methods which have been published in recent years and which are not always easily reproducible.[4] More recently, a palladium-catalyzed synthesis of esters **3** has been presented, which affords a weak *Z*-selectivity (*Z*/*E*: *ca* 60/40).[5] We now wish to report that *Z*-isomers can be readily obtained as major products in fair to good yields through the reaction between an aldehyde R-CHO **1** and diethyl 2-oxo-3-fluorobutan-1,4-dioate in its sodium salt form EtO_2C-CO-CF-CO_2Et^-, Na^+ **2** in THF.

Scheme 1

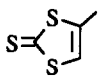


1a-i **2** **3a-i**

Previously, Bergmann *et al.*, extending the Gault results on the preparation of CH_2=CF-CO_2Et,[6] have shown that a mixture of an aldehyde, diethyl oxalate and ethyl fluoroacetate reacts in refluxed xylene in the presence of a weak base, giving rise to 2-fluoro-alkenoates **3**; however, no indication was given about the stereochemistry of this reaction.[7] Investigation of this method with ethanal revealed that the expected ester

CH_3-CH=CF-CO_2Et **3a** was mainly formed in the *Z*-form (*Z*/*E* : 84/16). This interesting result prompted us to carefully reexamine this reaction. Some modifications were made possible which simplify and improve the procedure, such as using the salt **2**[8] as reagent and THF as solvent. In these conditions, the reaction can be achieved at room temperature but requires a long time (over 12 h), the yield of **3** remaining limited; the best results were obtained by heating at reflux for 3 h.[9] On the other hand, a good stereoselectivity in the formation of esters **3** was observed from any aldehyde, the *Z*-isomers being the major products (*Z*/*E* ≥ 80/20). The results are summarized in the Table I.

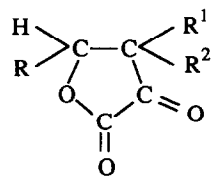
Table I - Formation of the esters R-CH=CF-CO_2Et **3**

N°	R	Yield (%)[a]	*Z*/*E*[b]
3a	CH_3	72 (lit[7a]: 61)	84/16
3b	CH_3-CH_2	53[c]	79/21
3c	CH_3-$(CH_2)_3$	76	79/21
3d	CH_3-CH=CH (*E*)	37	83/17
3e	C_6H_5	75 (lit[7a]: 68)	92/8
3f	4-Cl-C_6H_4	69[d] (lit[7a]: 74)	94/6
3g	C_6H_5-CH=CH (*E*)	24[e]	89/11
3h	1-naphthyl	58[f] (lit[7b]: 48)	89/11
3i		42[f]	98/2

a) Yield based on isolated (distilled or chromatographed) product. b) *Z*/*E* ratio determined by ^{1}H n.m.r. from integration of the ethylenic part of the crude product. c) Reaction performed at room temperature. d) 17% aldehyde recovered. e) 32% aldehyde recovered f) 37% aldehyde recovered.

By comparison with Bergmann's procedure, it first appears that this simple process may lead to 2-fluoroalkenoates **3** in similar or even better yields. On the other hand, the amount of recovered α,β-unsaturated aldehydes seems to suggest a lower reactivity of these systems than that of the aliphatic ones; the low yield obtained from crotonal **1d** may be explained by the fragility of the fluoro-dienic ester **3d** and also by the high sensitivity of crotonal towards basic agents.

This reaction is likely to proceed *via* an intermediate 2-oxobutyrolactone **4**, with R^1=F and R^2=CO_2Et, such a compound (R=iPr) having been isolated in a low yield (30%).[10] Nield has prepared a similar compound (R=Me or Ph, R^1=H, R^2=CO-Me) in high yield (>90%) from the reaction between ethanal (R=Me) or benzaldehyde (R=Ph) and the sodium salt of Me-CO-CH_2-CO-CO_2Et,[11] while a thermally unstable compound, the structure of which was postulated as **4** with R = CH_2=CH, R^1 = H and R^2 = CO_2Et, was obtained by

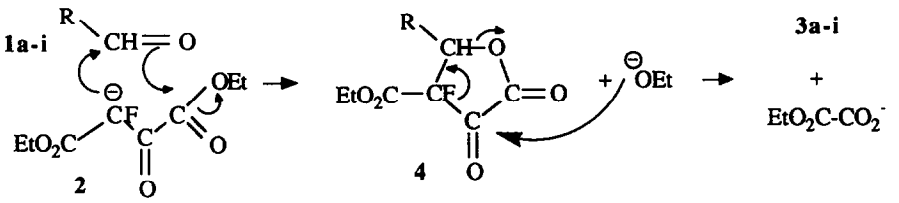


4

Gault *et al.* after reaction between acrolein and the potassium salt of EtO_2C-CO-CH_2-CO_2Et.[12] On the other hand, Ksander *et al.* have shown that such 2-oxobutyrolactones **4** are formed by reacting an aldehyde R-CHO with various oxalyl derivatives R'-CHE-CO-CO_2Et (E: keto, ester or nitrile group) in the presence of a base, with subsequent cleavage by aq. $KHCO_3$, leading to ethylenic compounds R'-CE=CH-R.[13]

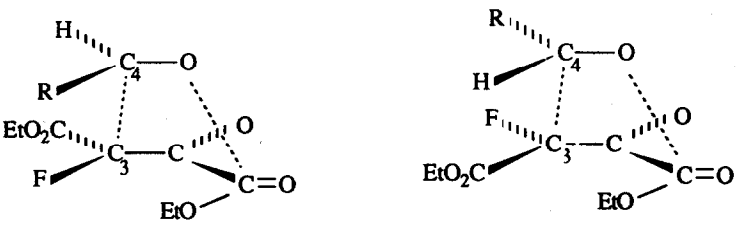
Our attempts to isolate fluorinated 2-oxobutyrolactones **4** (R^1=F, R^2=CO_2Et) were unsuccessful. From the reaction between ethanal **1a** or benzaldehyde **1e** with the salt **2** at 0°C for 1 h, followed by quenching with aq. HCl, a complex mixture was obtained whose composition could not be fully characterized in n.m.r.; however, the esters **3a** or **3e** were unambiguously identified in this mixture (only ~5% **3e** along with *ca* 75% unreacted **1e**). Moreover, after reaction at 80°C,[9] n.m.r. analysis of the crude reaction mixture showed that the ester **3e** was formed in nearly the same yield both before and after hydrolysis. These results might be accounted for as in Scheme 2, by cleavage of the fluorinated 2-oxobutyrolactone **4** by the EtO^- in the reaction medium, such a nucleophilic attack being facilitated by the strong electronegative character of the fluorine atom in the 3-position:

Scheme 2



In this process, the configurations of the 3-C and 4-C atoms of the 2-oxobutyrolactone **4** are fixed by the cyclization and should determine the stereochemistry of the fluoro-ethylenic esters **3**. In addition, as clearly shown by molecular frameworks, the approach between the aldehyde **1** and the salt **2**, which then induces the cyclization, should be controlled to some extent by the bulk of the ester group (3-C) and of the R-group (4-C), the best situation occurring when these two groups are preferentially located in a *trans*-like situation during this approach, irrespective of the geometry of the enolate **2** (see below Scheme 3).

Scheme 3



All our results appear to be well accounted for by the above hypothesis. In particular, we have observed (Table I) that the best Z-stereoselectivity was obtained from 4-formyl-1,3-dithiol-2-thione **1i**,[14] in which the formyl group is bonded to the bulkiest R-group in the series of aldehydes **1**.

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9 *General procedure*: a suspension of salt **2** (20 mmol) in THF (50 ml) was cooled to 0°C and aldehyde **1** (20 mmol) was added dropwise with stirring. After 1 h at 0°C, the mixture was heated at 80°C for 3 h and, cooled to room temperature, and most part of THF evaporated (or gently distilled in the case of low boiling ester **3a**). Diethyl ether (50 ml) and saturated aq. KHCO3 were added, with stirring at room temperature for 30 min. After the usual work-up, the *Z*/*E* ratio of ester **3** was determined by 1H n.m.r. on the crude mixture, which then was purified by distillation or by chromatography (hexane-ether 9:1).

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