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Reaction of lithium enediolates with perfluoroketene dithioacetals. Synthesis of α-trifluoromethyl γ-dicarboxylic acid derivatives☆

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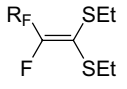
Abstract—The reaction of perfluoroketene dithioacetals with dianions of carboxylic acids proceeds through the substitution of the vinylic fluoride. The preparative value of this reaction depends strongly on the reaction and work-up conditions, the optimisation of which led to use LDA as a base and multiple extraction techniques. The overall process may be considered as a formal synthesis of α-trifluoromethyl γ-dicarboxylic acid derivatives.

Fluorine substituents significantly change the physicochemical properties, the chemical reactivity and the biological activity of molecules when compared to their nonfluorinated analogues.[1,2]

Perfluoroketene dithioacetals are easily prepared interesting intermediates.[3] Owing to both a normal and umplong reactivity, they proved to be versatile building blocks for the synthesis of fluorosubstituted polyfunctional compounds. More particularly, compound **1a**[4] and the higher homologue **1b**[5] were used as starting materials for various elaborated perfluoroalkylated heterocyclic compounds.



1a $R_F = CF_3$
1b $R_F = C_2F_5$

The applications of **1** reported so far were mainly based on the substitution of the vinylic fluoride by a ketone enolate, leading to a key intermediate: a γ-keto-α-trifluoromethyl carboxylic acid derivative.[4,5] It was interesting to extend the scope of this chemistry to enolates of carboxylic acid derivatives. At the same time as the study of the reaction of **1a** with ethyl acetate enolate and/or other equivalents,[6] we have investigated its reaction with enediolates, which could give a direct access to α-trifluoromethyl γ-dicarboxylic acid derivatives where the two carboxylic moieties are differentiated. We report here the results of this study, including an optimisation of the reaction conditions and work-up.

It is well known that carboxylic acids are synthetically useful building blocks because, after double deprotonation, they afford enediolates that react with several electrophiles under adequate conditions.[7,8] Lithium dialkylamides are generally used as bases to generate lithium enediolates and dienediolates[9–11] due to their strength and low nucleophilicity (especially when derived from hindered amines) and to their solubility in nonpolar solvents.[11,12] In these solvents, lithium enolates generally exist as complex ion-pair aggregate structures whose metal centre may be coordinated to solvent molecules or other chelating ligands such as the amines resulting

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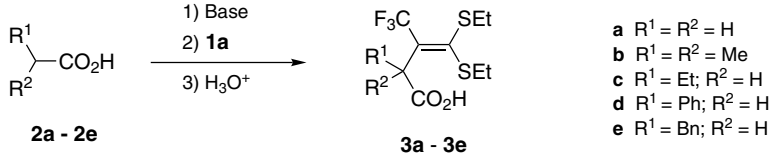


Scheme 1.

from the deprotonation of the acid by the lithium amide. The available data confirm the complexity of these aggregated reactive species and that many factors can affect them and consequently their reactivity.[8,12,13]

The reaction pathway and reactants are depicted in Scheme 1. The base used to generate the enediolate plays a crucial role, as shown in Table 1.

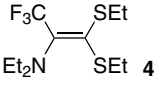
The optimisation of the reaction conditions are summarised in Table 1. Although lithium diethylamide (LDE) is the most common base in enediolate chemistry, the vinylic fluoride was substituted by this lithium amide, as expected,[14] to give compound **4** (see Table 1, entries 2 and 7).

To minimise this problem, we used a sub-stoichiometric amount of amine which in most cases, allows the formation of enediolates, from the corresponding acid, without Barbier's reduction or Michael adduct formation.[9] The amino substituted derivative was no longer present but the yield of fluorinated acid was not improved (entry 2). Consequently, different amides were tested, chosen according to their steric hindrance. The best results were obtained using LDA in stoichiometric amount (entries 4 and 10). The standard reaction time was established to be 1 h, as longer reaction time does not improve the results.

Table 1. Addition of acetic (**2a**) and butanoic (**2c**) acid dianions to **1a**

Entry	Acid	Amide	Equiv. amide	Time (h)	Product **3** (Yield %)
1	**2a**	$LiNEt_2$	2	1	**3a** (13)
2	**2a**	$LiNEt_2$	0.6	4	**4** (6[a])
3	**2a**	$LiNEt^2$	2	1	**3a** (22)
4	**2a**	$LiN(i\text{-}Pr)_2$	2	1	**3a** (50)
5	**2a**	LiAZA	2	1	**3a** (5)
6	**2a**	LiAZA	0.6	1	**3a** (2)
7	**2c**	$LiNEt_2$	2	1	**4** (44[a])
8	**2c**	LiHMDS	2	1	**3c** (25)
9	**2c**	LiTMP	2	1	**3c** (60)
10	**2c**	$LiN(i\text{-}Pr)_2$	2	1	**3c** (67)

The amine was evaporated in vacuo prior to the addition of **1a**.



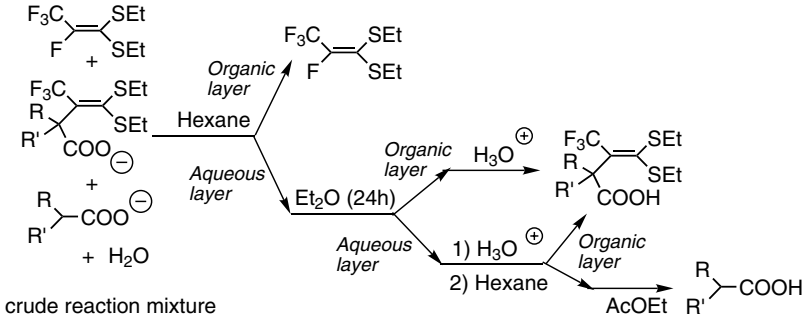
4

Abbreviations: AZA: 1,3,3-trimethyl-6-azabicyclo(3.2.1)octane; HMDS: hexamethyldisilazane; TMP: 1,1,5,5-tetramethylpiperidine.
[a] Neutral fraction.

Another point to be considered is that, generally speaking, fluorinated compounds are more volatile and less polar than nonfluorinated analogues.[1] Accordingly, the reaction work-up had to be optimised compared to the standard procedure where neutral and acidic fractions are obtained. The first one, containing only neutral and basic products, came from the direct extraction of the aqueous crude mixture. The resulting aqueous phase was acidified and extracted to yield the crude acidic fraction where nearly pure acidic products are usually obtained.[15] When this standard work-up was applied to the reaction with **1a**, the neutral fraction contained an important amount of substitution product as its carboxylate. The work-up was then modified as follows: see Scheme 2.[16]

Application of this work-up, with LDA as a base in stoichiometric amount, led to the results summarised in Table 2.[17] Yields are moderate to high, especially when considering that both the starting acid and the perfluoroketene dithioacetal may be recovered, in different steps of the work up and are pure enough to be reused.

In summary, we have found a new application of the chemistry of dianions of carboxylic acids. The overall process may be considered as a formal synthesis of α-trifluoromethyl γ-dicarboxylic acid derivatives, where one carboxylic function is masked,[4,6] and constitutes a new development of perfluoroketene dithioacetal **1** as a



Scheme 2.

Table 2. Reaction of carboxylic acid dianions with **1a** under optimised conditions

Entry	Starting acid	Acid product (%)	**1a** Recovered in the neutral fraction (%)
1	**2a**	**3a** (50)	24
2	**2b**	**3b** (53)	14
3	**2c**	**3c** (67)	22
4	**2d**	**3d** (62)	25
5	**2e**	**3e** (92)	8

versatile building block towards the synthesis of multifunctionalised perfluoroalkylated derivatives.

Acknowledgements

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16. *General procedure*: *n*-Butyllithium (from Fluka, 1.6 M in hexane, 2.50 mmol) is introduced into a previously argon purged reaction flask. Hexane is evaporated under vacuum and THF (2 mL) followed by the amine (2.25 mmol) are added at −78 °C. The mixture is stirred for 15 min at 0 °C. The acid **2** (1.13 mmol) in THF (1 mL) is slowly added at −78 °C. After 1 h at 0 °C, the perfluoroketene dithioacetal **1a** (1.13 mmol) in THF (1 mL) is slowly added at −78 °C. The solution is stirred at room temperature for 1 h (4 h for phenylacetic acid) and quenched with water (15 mL). The reaction mixture is extracted with hexane (3 × 15 mL). This fraction yields mainly unreacted ketene dithioacetal. The aqueous layer is continuously extracted with diethyl ether for 24 h. This fraction is washed with concentrated HCl until pH = 1 to give the condensation product **3** with chromatographic purity. The remaining aqueous fraction is acidified with concentrated HCl up to pH = 1 and then extracted with hexane (3 × 15 mL). This fraction leads to further product **3** along with 5–10% (NMR) unreacted acid **2** that, when necessary, can be purified by column chromatography. The remaining aqueous fraction is re-extracted with ethyl acetate (3 × 15 mL) leading to pure starting acid.
17. Compounds **3a**–**e** gave satisfactory NMR (^{1}H, ^{13}C, ^{19}F), IR, MS and elemental analyses. Selected data for **3d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.23 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, CH_3), 1.27 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H, CH_3), 2.8 (m, 2H, SCH_2), 2.9 (m, 2H, SCH_2), 6.01 (s, 1H, C*H*–CO_2H), 7.2–7.4 (m, 5H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.9 (s, CH_3), 15.2 (s, CH_3), 28.7 (s, SCH_2), 29.3 (s, SCH_2), 53.6 (m, *C*H–CO_2H), 123.3 (q, $^{1}J_{CF}$ = 275.6 Hz, CF_3), 127.8 (s, CH), 128.8 (s, CH), 129.1 (s, CH), 134.8 (q, $^{2}J_{CF}$ = 28.1 Hz, =*C*–CF_3), 135.5 (s, C_q), 147.4 (m, *C*=C–CF_3), 176.7 (s, CO_2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ (ppm) −53.4 (s). IR (NaCl) ν (cm^{-1}): 3500–3000, 2988, 1712, 1549, 1451. HRMS: *m/z* calcd for $C_{15}H_{17}F_3O_2S_2$ 350.0622. Found 350.0622.