Direct Fluorination of 1,3-Dicarbonyl Compounds

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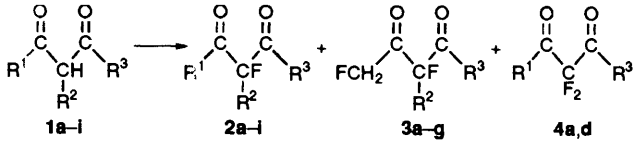
1,3-Dicarbonyls, such as 1,3-diketones and 1,3-ketoesters, react directly with elemental fluorine at room temperature to give the corresponding 2-fluoro- and, in some cases, 2,2-difluoro-compounds in high yield.

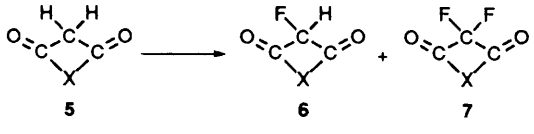
The efficacy of many pharmaceuticals and agrochemicals is often enhanced or is dependent on the presence of a single fluorine atom in the structure.[1] Frequently, such compounds are synthesised from smaller molecules in which fluorine is located at specific sites. Elemental fluorine is normally regarded as being too reactive for site specific fluorination reactions and many fluorinating agents have been developed in order to make desirable fluorine containing 'building blocks'.[2,3] In this context, the preparation of 2-fluoro-1,3-dicarbonyl compounds has aroused much interest and they have been synthesised by treating the parent dicarbonyls or their enolates with one of the many electrophilic fluorinating agents (themselves made using elemental fluorine) which have been developed recently.[4–8] They have also been prepared by the action of fluorine on the silyl enol ethers of the parent 1,3-dicarbonyls at −78 °C in CCl_3F.[9] We now report the surprising finding that the simple direct reaction between elemental fluorine and certain 1,3-dicarbonyl compounds can be used to synthesise 2-fluoro-1,3-dicarbonyl compounds in high yield.

When fluorine (0.05 mol) diluted to 10% *v/v* with nitrogen is passed through stirred solutions of 1,3-dicarbonyls (0.025 mol in 50 ml formic acid) (Schemes 1 and 2) at 10–15 °C over two hours, the results summarised in Tables 1 and 2 are obtained.

As indicated in Table 1, the fluorination of compounds **1a** and **1d** gives significant amounts of difluorinated products, but the interesting feature of this is that more of the difluoro-compounds in which the second fluorine atom has replaced a hydrogen on the terminal methyl group, **3a–d**, are produced than those in which it has replaced the second methylenic hydrogen, **4a–d**. Generally, we find that introduction of a second fluorine is very much slower than the first and even after several hours exposure to fluorine the monofluoro-compounds are the main products. On the other hand, cyclic 2-fluoro-1,3-dicarbonyls appear to be more reactive and difluorination is relatively easily accomplished (Scheme 2, Table 2). 1,3-Diketones are more reactive than the corresponding 1,3-ketoesters, and diesters such as diethylmalonate fail to react under these conditions. While in the work described here, formic acid was used as the solvent, the use of acetonitrile gives similar results.



Scheme 1



Scheme 2

The mechanism by which these reactions proceed has been investigated by using NMR to measure the rate at which hydrogen is displaced from the 2-position in a series of 1,3-ketoesters when these compounds are dissolved in DCO_2D. The enol content of these compounds under the conditions of the reaction has also been measured. From this information and a consideration of the percentage conversions over the two hour period of the reactions (Table 1), it is concluded that the mechanism by which fluorination of 1,3-dicarbonyls occurs is similar to that for the reaction of ketones with other halogens. Fluorine first reacts very rapidly with any enol already present in solution. Thereafter, the rate of fluorination is governed by the rate of enol formation. Thus, although the enol content of ethyl acetoacetate is less than 3% in formic acid, the conversion to the 2-fluoro-compound after 2 h exposure to fluorine is 60% and when the compound is treated with the same amount of fluorine over 4 h, the conversion rises to 80%. The enol content of ethyl-2-methyl acetoacetate is similar to that of ethyl acetoacetate but its lower rate of enolisation accounts for the lower conversion. In the case of ethyl-1-chloroacetoacetate which has a significant enol content in formic acid but where the rate of enolisation is very slow, almost all of the reaction occurs over the first 15 min of exposure to fluorine, after which time the enol present at the outset has reacted and little more fluorination occurs.

Table 2 Reaction of elemental fluorine with cyclic 1,3-dicarbonyl compounds

5	X	**6** Yield (%)	**7** Yield (%)	Conversion (%)
a	$-CH_2CMe_2CH_2-$	10	50	>95
b	–NHCONH	50	30	>80
c	–NMeCONMe–	70	15	25

Table 1 Reaction of elemental fluorine with acyclic 1,3-dicarbonyl compounds

1	R^1	R^2	R^3	**2** Yield (%)	**3** Yield (%)	**4** Yield (%)	Conversion (%)
a	Me	H	Me	70	11	3	90
b	Me	Me	Me	76	9	—	90
c	Me	Cl	Me	65	7	—	85
d	Me	H	OEt	80	10	*ca.* 1	60
e	Me	Me	OEt	85	5	—	25
f	Me	Cl	OEt	85	5	—	15
g	$-(CH_2)_4-$		Me	70	10	—	95
h	$-(CH_2)_4-$		OEt	90	—	—	90
i	$-(CH_2)_2OCO-$		Me	80	4	—	70

These results indicate that elemental fluorine has been greatly underestimated as a reagent for site specific fluorinations and that in these systems fluorine reacts in a manner similar to that of other halogens with ketones.

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