Mono-hydrofluorination of Electrophilic Alkynes by the Liquid Biphasic CsF–H_2O–DMF System (DMF = N,N-dimethylformamide)

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CsF induces the addition of HF in fair yields to activated acetylenic triple bonds in a DMF–water biphasic medium (DMF = N,N-dimethylformamide); in a homogeneous DMF–water mixture, no addition is observed.

Many efforts are still devoted to develop new ways of access to organofluorine compounds on account of their interesting properties in applied chemistry and in biochemistry.[1,2] More or less sophisticated methods of preparation of functionalized fluoro-vinylic derivatives are now available;[3] among them, the very clean mono-hydrofluorination of electrophilic alkynes through reaction of onium dihydrogen trifluoride salts, which was recently described by one of us.[4] We now report that this nucleophilic addition of HF can simply be performed by using CsF as the source of fluoride ion.

CsF is known to react in an aprotic medium with highly electron-deficient alkynes such as diethyl but-2-yne-dioate or perfluro-but-2-yne, the transient fluoro-vinyl carbanion promoting the anionic polymerization of the starting alkyne or being trapped by a strong non-protic electrophile.[5,6,7] Under such conditions, only small amounts of diethyl fluoro-fumarate can be formed after the slower proton abstraction from sulpholane used as the solvent.[5]

In order to generate and then protonate the fluoro-carbanion E–C$^-$=CF–E′ after reaction of an electrophilic alkyne E–C≡C–E′ (**1**) with CsF, it was therefore necessary to find a system in which two separate species may display, without strong interaction, two apparently antagonistic properties; one behaving as an efficient source of nucleophilic fluoride ion, *e.g.* CsF, and the other as a source of H^+, whereas the well-known protophilicity of F^- is expected to preclude such a possibility.[8,9]

This problem was solved by using a liquid biphasic medium. Stirring a heterogeneous mixture of dimethyl but-2-yne-dioate (**1a**) (10 mmol) in *N,N*-dimethylformamide (DMF) (150 ml) and caesium fluoride (20 mmol) in a very small amount of water (80 mmol) (method A) for 40 min at 80 °C brings about the hydrofluorination of the C≡C bond *via* a phase-transfer process, the water serving as the protonating agent, while the resulting caesium hydroxide is driven into the non-miscible aqueous phase (Scheme 1). The corresponding HF-adduct (**2a**) is obtained in a 67% yield (isolated product) as a mixture of (*Z*)- and (*E*)-isomers in the molar ratio 85/15.

In order to decrease possible side reactions (*e.g.* saponification), hydroxide ions can be neutralized by accomplishing the reaction in the presence of KHF_2 [(**1a**), CsF and KHF_2 in 1 : 3 : 1.4 mol ratio; method B], but the yield of (**2a**) is only improved by *ca.* 5%.

When applied to various electrophilic alkynes (**1b**—**g**), this mainly *trans*-addition of HF always proceeds in a fully regioselective way (F-addition to the β-carbon atom with respect to the stronger electron-withdrawing group, E), and no bis-addition is observed, as shown by the results in Table 1.

The amount of water plays a crucial role in this process. In a homogeneous DMF–H_2O mixture that contains more water, no HF addition is observed. On the other hand, in the absence of water, CsF mainly induces the polymerization of the starting acetylenic compound (**1a**) and only traces of HF-adduct (**2a**) are formed, as already reported in the case of (**1b**) in sulpholane.[5]

The influence of the alkali metal cation has also been studied. When M^+F^- salts (M = Cs, Rb, K, Na, Li) are reacted with (**1a**) (see method A, 80 °C, 40 min), (**2a**) is obtained in the following respective yields: 67, 40, 37, 0 and

DMF phase: E–C≡C–E′ (**1a**—**g**) $\xrightarrow{H_2O}$ E–CH=CF–E′ (*Z* + *E*) (**2a**—**g**)
H_2O phase: CsF → CsOH

a; E = E′ = CO_2Me
b; E = E′ = CO_2Et
c; E = CO_2Me, E′ = Ph
d; E = CO_2Et, E′ = Ph
e; E = CHO, E′ = Ph
f; E = CN, E′ = $CH(OEt)_2$
g; E = CHO, E′ = $CH(OEt)_2$

Scheme 1

Table 1. Results for the *trans*-addition of HF to various electrophilic alkynes.

	HF-adduct	Yield/ %	*t*/h	*T*/°C	(*Z*)/(*E*) mol ratio
Method A	(**2b**)	41	3	65	83 : 17
	(**2f**)	35	2	65	100 : 0
	(**2g**)	10	3	50	90 : 10
Method B	(**2c**)	62	10	120	95 : 5
	(**2d**)	45	12	120	100 : 0
	(**2e**)	40	0.5	120	95 : 5

0%. These results are in agreement with the preferential solvating effect of DMF *vs.* large alkali metal cations,[10] and also fit with the cation-dependent nucleophilicity of M^+F^- salts in DMF.[11,12] Thus it seems likely that in our process, despite $F^- \cdots H_2O$ hydrogen bond associations in the aqueous phase, DMF may favour the extraction into the organic phase of the poorly soluble M^+F^- salts possessing a large cation. In support of this statement, it was observed that, when the reaction is performed with KF, adding a catalytic amount of CsF does not improve the yield of (**2a**).

In conclusion, owing to the phase-transfer process which only makes possible the surprising overall conversion of a weak base (F^-) into a strong one (OH^-), it appears that the present methodology constitutes a straightforward access to highly functionalized fluoro-vinylic compounds. In a homogeneous DMF–H_2O mixture, the strong $F^- \cdots H_2O$ solvation and the CsOH solubility do not allow this simple conversion to occur.

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