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The Hosomi–Sakurai allylation in hexafluoroisopropanol: solvent promotion effect

Svetlana P. Panchenko,[a] Sofia A. Runichina[a] and Vasily V. Tumanov*[b]

[a] *Moscow Chemical Lyceum, 111033 Moscow, Russian Federation. Fax: +7 495 362 3440*
[b] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: vasilii_tumanov@mail.ru*

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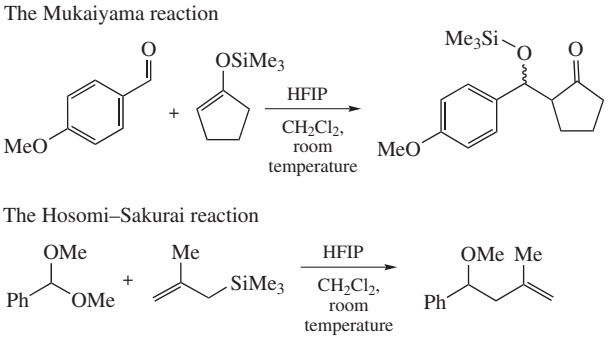
Hydrogen bond donating capacity of hexafluoroisopropanol was shown to be responsible for both the formation of its stoichiometric complexes with aldehydes and acetals and subsequent facilitation of their reactions with allylsilanes.

Our recent investigation[1] revealed that hexafluoroisopropanol (HFIP) while used as a solvent is capable of promoting such important C–C couplings as Mukaiyama and Hosomi–Sakurai reactions in the absence of any additional catalysts (see examples in Scheme 1).



Scheme 1

According to an ample literature evidence[2] the above type reactions as well as a plethora of other classical electrophilic transformations require the application of strong Lewis or Brønsted acid as the initiators. Numerous mechanistic studies revealed that the mechanism of these reactions involves the activation of an electrophile *via* its transformation into the covalent reactive carbocationic intermediate under the action of the above initiators.[3] In view of these data the disclosed property of HFIP seemed to be rather bizarre since this solvent has never been listed among Lewis acids and its Brønsted acidity is known to be quite low (pK_a = 9.3, *cf.* pK_a = 4.8 for acetic acid).

Previously we have shown that in HFIP solution neither aldehydes nor acetals undergo conversion into the respective hydroxy- or alkoxycarbenium ion intermediates.[1] Hence it was suggested that the promotion effect of HFIP in the reactions shown in Scheme 1 could be ascribed to the ability of this solvent to serve as a powerful hydrogen bond donor toward various acceptors in conjunction with its high total polarity and low nucleophilicity.[4]

The observed unusual profile of the HFIP promotion effect and its promising synthetic potential most certainly warranted additional studies. Herein we present the results of our current investigation in this area.

According to the protocol described in the cited paper[1] all reactions were carried out in of 4:1 (v/v) HFIP–DCM[†] solvent system with total concentration of each reactant ~1 mol dm^{-3}. Thus, in the most cases HFIP was employed in 8–10 equiv. excess to electrophile (E).[‡] In our further studies we disclosed that dilution of the reaction mixture with DCM (1:1, v/v) resulted in a dead stop of the reaction. Similarly a dramatic retardation effect was produced by the decrease of HFIP/E ratio from 8:1 to 1:1. Hence one may conclude that not only the presence and amount of the inert co-solvent but the ratio of E/HFIP as well could critically affect the efficiency of the overall reaction outcome.

These results prompted us to undertake a more detailed study of HFIP activation effects with an ultimate goal to get an answer to a major question: whether it is possible to draw a borderline between two most obvious facets of the HFIP promoting action, namely, its role as an initiator and as a medium?

As a model we have chosen the Hosomi–Sakurai reaction of aldehydes **1** and **2** and acetals **3** and **4** employed as electrophiles (E) with allylsilanes **5** and **6** (Nu). Our methodology was based on the use of ^{1}H (and to a lesser extent ^{13}C) NMR spectroscopy to register first the changes brought by the dissolving of a chosen E component in neat HFIP[§] and then, after an introduction of the respective Nu, to monitor the progress of allylation reaction.

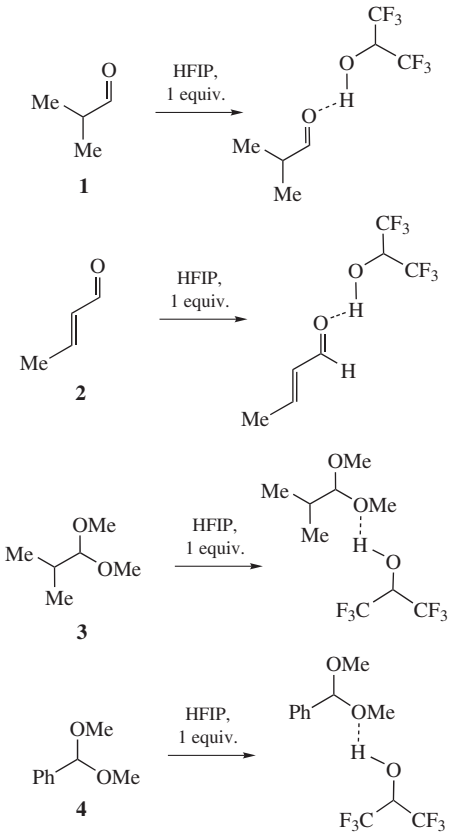
First of all we had to address the problem of hydrogen bond formation in the system E/HFIP. Hydrogen bonding may result in changes of spectral parameters of both electrophile and HFIP. According to the literature data formation of hydrogen bonded species *via* an interaction of HFIP with various acceptors could be detected by significant downfield shift of hydroxyl proton of HFIP,[5] however, no such data were available for aldehydes and acetals.

We have established that ^{1}H NMR spectra pattern of aldehydes **1** and **2** and acetals **3** and **4** dissolved in the neat HFIP did not reveal any significant changes as compared to the basic spectra of these compounds in $CDCl_3$. At the same time the hydroxyl proton signal of HFIP underwent a rather significant downfield shift upon the addition of E component. The maximum deshielding was

[†] The latter additive was needed due to limited solubility of some substrates in pure HFIP. The 'ideal' ratio of the co-solvents was established as 4:1 (v/v), respectively.

[‡] For example, an interaction of isobutyric aldehyde (E) with methallylsilane (Nu) (E/Nu = 1:1.2) in the above solvent system proceeded readily at ambient temperature to furnish the expected allylation product in a nearly quantitative yield.

[§] The performing of NMR studies should be commented separately. In the present work well-miscible with HFIP substrates were employed and NMR monitoring was accomplished for 'pure' mixtures – only HFIP and substrate(s) – in order to keep the system properties unchanged and to exclude any side influence. Deuterated co-solvent ($CDCl_3$) was sometimes added in a minimal amount as a chemical shift standard.



Scheme 2

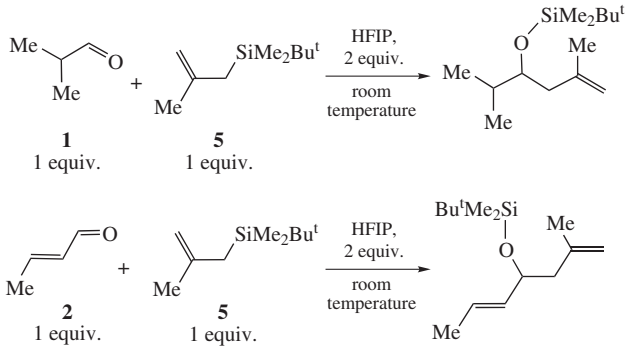
observed for 1:1 HFIP/E mixture, its value ($\Delta\delta$ = 1.6±0.1 ppm) being rather close to the data reported previously for a number of hydrogen bonded complexes of HFIP with various acceptors.[5,6]

It is also known that deshielding of carbonyl resonance signals in ^{13}C NMR spectrum might be a useful criteria for the characterization of hydrogen-bonding interactions of carbonyl group with hydrogen bond donors.[6,7] We have established that ^{13}C NMR spectra of the solutions of **1**–**4** in HFIP in the solute/solvent ratio 1:1 reveal a rather significant downfield shift of the carbonyl or acetal carbon signals. The magnitude of these effects, $\Delta\delta$ = 6–7 ppm for the carbonyl of aldehydes **1** and **2** and $\Delta\delta$ = 3–4 ppm for the acetal carbon of **3** and **4** is close to the values reported earlier for the valerolactone and related carbonyl derivatives.[6] Further increase of HFIP amount does not lead to any changes in ^{13}C NMR spectra of these compounds.

Hence the observed deshielding effects are not due to some solvent effects and could be taken as an evidence in favor of stoichiometric interaction of HFIP with E in 1:1 ratio (see Scheme 2).

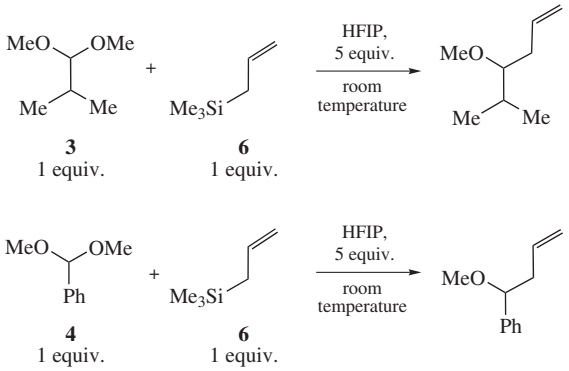
Next, we have studied the dependence of efficiency of allylation reaction on the amount of HFIP employed using ^{1}H NMR spectra to monitor the reaction course. Initial experiments disclosed that no reaction occurred at ambient temperature upon the addition of allylsilane **5** to the 1:1 mixture of any electrophile of the set **1**–**4** with HFIP. Moreover, ^{1}H NMR data clearly indicated that no reaction between **1** and **5** took place even upon the reflux of 1:1:1 mixture HFIP/E/Nu overnight. At the same time, addition of 1 more equivalent of HFIP to this mixture resulted in a rather fast formation of the expected allylation product (according to ^{1}H NMR data reaction went to the completion within 2 h at ambient temperature, see Scheme 3). Similar observations were made for the interaction of **2** with **5**.

On the contrary, in case of allylation of acetals **3** and **4** with allylsilane **6** no reaction startup was observed in 2:1:1 mixture HFIP/E/Nu under the same conditions. Further increase of HFIP amount in the reaction mixture (up to 3:1:1 ratio) was required in



Scheme 3

order to trigger these reactions. However much to our surprise, the process stopped at 60% conversion and no changes were detected in ^{1}H NMR spectra pattern upon the storage of the mixture for 24 h. Full conversion of starting materials was achieved only after additional amount of HFIP (up to 5:1:1 ratio) was introduced (Scheme 4).



Scheme 4

Thus, we came across a rather paradoxical phenomenon, namely, the dramatic acceleration of bimolecular reaction with the decrease of reactants concentration. The above data could be accounted for by suggesting an involvement of several molecules of HFIP in the formation of the rate-determining transition state of the Hosomi–Sakurai reaction in this solvent.

Certainly, the detailed kinetic and computational studies of this process are required in order to verify the advanced suggestions. Meanwhile, an evidence attesting to its validity could be found in the relevant results obtained by the Berkessel group which refer to the dramatic accelerating effect on the rate of olefin epoxidation by hydrogen peroxide caused by the presence of HFIP (up to 10^6-fold rate increase).[8] The authors disclosed that under these conditions a rate order 2–3 with respect to the concentration of HFIP is observed and hence concluded that 'two to three molecules of HFIP are involved in the rate-determining step of the kinetically dominant reaction path'.[8(*a*)]

The data obtained in the present work allowed us to clearly discriminate two major factors responsible for the observed effect of HFIP as a 'magic' solvent capable of promoting Hosomi–Sakurai reaction and a number of other Friedel–Crafts like electrophilic transformations[1] under acid-free conditions. Firstly, HFIP serves as an activator of the starting electrophile due to formation of 1:1 hydrogen bonded complex E-HFIP. Next, HFIP participates as an additional stoichiometric component facilitating the reaction of the above complex with a nucleophilic reactant. In this case the polar transition state stabilization could be achieved by the involvement of the conglomerate of several hydrogen-bonded

HFIP molecules in a mode similar to that suggested by Berkessel *et al*.[8]

Thus, we may conclude that the underlying cause of the observed unique activity of HFIP is due to the multifunctional pattern of its donating capacity. Besides the direct binding with an electrophile (conventionally designated as a static effect) HFIP exhibits even more important capacity to serve as a bank of hydrogen bonds available for the use when required (dynamic effect).

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