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2D Ultrafast HMBC: A Valuable Tool for Monitoring Organic Reactions[§]

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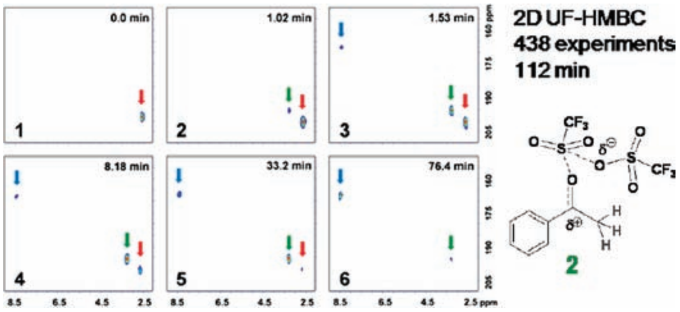
ABSTRACT



Ultrafast 2D HMBC spectroscopy permits real-time monitoring of a reaction based on the structural changes produced in a carbonyl carbon atom. This new technique was used to study the reaction of ketones, nitriles, and Tf_2O, affording relevant information about new intermediates and kinetic data.

Traditional *n*D NMR experiments are collected as an array of 1D scans and are intrinsically time-consuming.[1] Different proposals to speed up *n*D NMR spectroscopy have been described in recent years.[2] Among them, ultrafast-NMR spectroscopy (UF-NMR) alone or coupled with other methodological elements into a single scheme has shown its capability of delivering any type of *n*D spectrum in a single scan by spatially encoding the indirect-domain interactions.[3] Real-time monitoring of dynamic chemical systems, i.e., organic reactions, can be done as they happen.[4]

Recently we have studied the synthesis of alkylpyrimidines from aliphatic ketones by two-dimensional UF-TOCSY, which has permitted the collection of a complete multidimensional data set within a single continuous acquisition. The evolution of the reactants from early stages of the reaction, the presence of different nitrilium-type intermediates, and the generation of reaction products can be monitorized.[5] Despite these important findings, no direct information regarding structural changes in the carbonyl carbon atom was obtained. The reason is clear. Since it is a quaternary carbon, its evolution cannot be detected using 2D homonuclear sequences such as COSY or TOCSY or heteronuclear such as HSQC. On the other hand, a UF-HMBC pulse sequence can offer direct and more precise information about the structural changes that take place on the carbon core and protons attached at neighbor positions. Chemical shifts obtained from 2D HMBC $^2J/^3J$ correlations should permit real-time observation of the changes produced. This information can be

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[§] Dedicated to Prof. Antonio García Martínez on the occasion of his retirement.

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very important since the carbonyl carbon atom plays a decisive role in numerous organic reactions.

Although the chemistry of triflic anhydrides and their reactions with carbonyl compounds is well-known, some mechanistic questions still remain open.[6] Thus, it has been accepted for many years that the reaction consists of the electrophilic attack of the anhydride on the carbonyl oxygen; this results in the formation of the short-lived (trifluoromethanesulfonyl)carbenium ion (**2**) (Figure 1). Despite this no data about the structure and kinetic behavior of the crucial intermediate **2** are yet known. Depending on the nature of the carbonyl compound and the reaction conditions, there are different possibilities for **2**; it can lead directly to vinyl triflates or to different products after trapping by an external nucleophile.

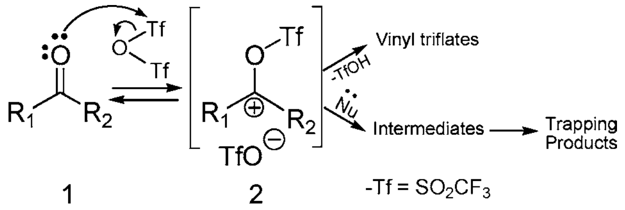

Figure 1. Reaction possibilities from ketones and triflic anhydride.

In this paper we studied the organic reaction described above and monitored how the carbonyl carbon atom evolves during the process. Our aim is to identify possible intermediates formed. We chose a simple aliphatic-aromatic ketone, acetophenone, as the model compound and studied its reaction with triflic anhydride in the presence of an excess of acetonitrile acting as nuclephile and the solvent. This leads to pyrimidines as main products. Labeled ^{13}C-carbonyl-acetophenone and [D$_3$]acetonitrile were used as reactants. ^{13}C-Carbonyl-labeled ketone ensures the detection of short life intermediates and overcomes sensitivity problems. Attempts done with unlabeled ketones failed. The use of [D$_3$]acetonitrile eliminates the neccessity of solvent suppression. The reaction was carried out inside a standard 500 MHz spectrometer with conventional hardware and a 5 mm NMR tube. The reactants were added with a fast mixing device. For experimental details and procedure see Supporting Information.

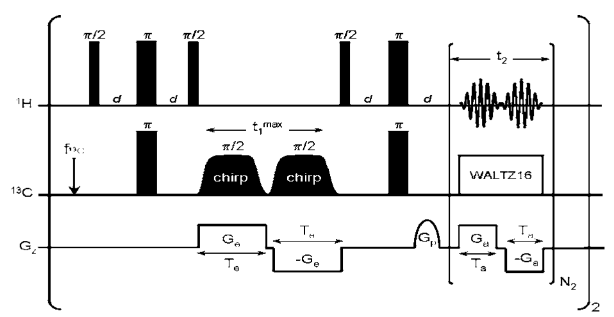

Figure 2. Ultrafast two-dimensional HMBC implemented to monitor changes on the carbonyl carbon atom.

Figure 2 shows the scheme of the 2D UF-HMBC sequence used. This sequence consists basically of a continuous spatial encoding ultrafast HSQC sequence in which the delay d is set to 25 ms in order to monitor ^2J and ^3J couplings of 10 Hz.[7]

In this UF scheme, contrary to traditional approaches, the spectral widths in both indirect and direct dimensions are dependent on each other. The greater the spectral width that must be covered in both dimensions, the poorer the digital resolution in the indirect domain.[8] Furthermore, the spectral width and therefore the resolution in the indirect domain depends on the strength G_a and duration T_a of the decoding gradient, and both of these are limited. Because a wide spectral range in the indirect domain needed to be covered to detect the possible intermediates, we decided to monitor two different spectral windows in this dimension. For this purpose we alternated the same sequence with different indirect dimension frequency offsets. The acquisition of these two data sets was repeated during the progress of the reaction.

A total of 219 UF-HMBC spectra for each spectral window were recorded over a total time of 112 min. Each single spectrum was measured for 5.37 s, and a measurement was repeated every 10 s. For acquisition conditions see Supporting Information.

Figure 3 shows a series of six representative 2D UF-HMBC spectra recorded (spectra 1−6). These spectra correspond to the first window studied. The ranges examined were 210−150 ppm for ^{13}C, which covers the carbonyl region and 9−2 ppm for ^{1}H. Spectra were numbered 1−6 (referred to as HMBC-1, etc). Cross-peaks assigned to starting and final products were confirmed using standard 1D and 2D spectra (see Supporting Information).

Spectrum HMBC-1 (0.0 min) corresponds to the solution of ketone **1** in [D$_3$]acetonitrile before the addition of Tf_2O. HMBC-1 shows a cross-peak at 198.9−2.56 ppm due to the ^2J coupling between the carbonyl carbon and the methyl protons of **1** (red arrow). The addition of Tf_2O produced a small change in the position of the cross-peak from **1**. In HMBC-2, taken 1.02 min after the addition, a new cross-peak appeared at 195.2−3.26 ppm (green arrow). This peak intensified in HMBC-3 (1.53 min), decreased clearly in HMBC-5 (33.2 min), and remained close to the detection limit in HMBC-6 (76.4 min). Simultaneously, the cross-peak (167.4−8.38, blue arrow) that belongs to the pyrimidine **5** increased its intensity (HMBC-3 to HMBC-6). The signal from **1** decreased (HMBC-1 to HMBC-5) and is absent in HMBC-6.

In our opinion, this new cross-peak (green arrow) depicted in Figure 3 belongs to the complex **2** formed from ketone **1** and triflic anhydride. The rise and fall of **2** during the reaction clearly shows its character as intermediate. Structures of **1** and **2** are similar and therefore produce cross-peaks close to each

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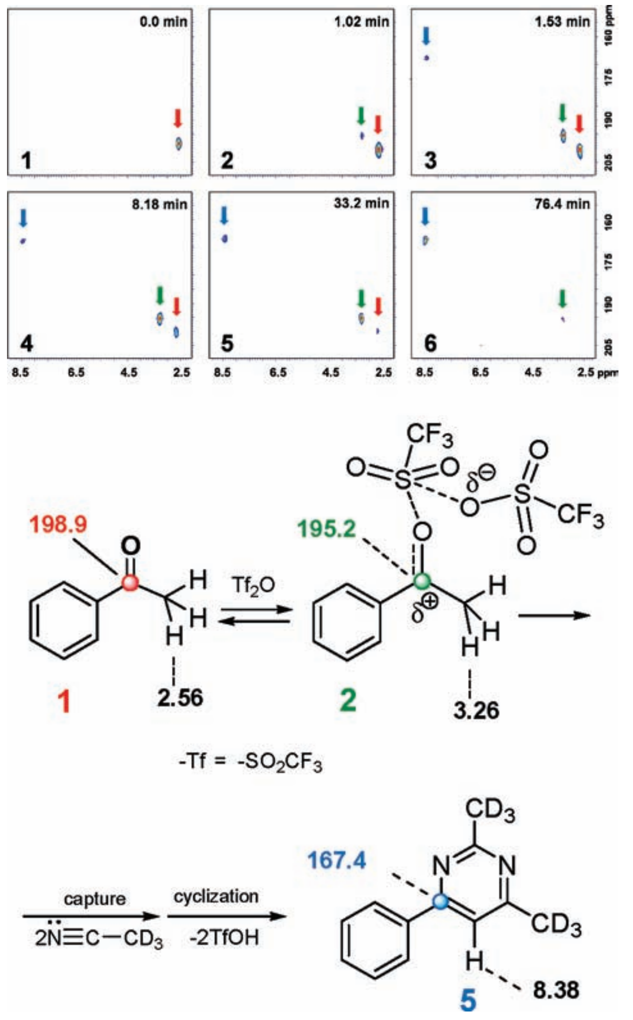

Figure 3. A series of 6 UF-HMBC experiments (1−6) taken at different times throughout the reaction (scale is in ppm) and shifts from the participanting reactant **1**, product **5**, and intermediate **2**.

other. The structure of benzylic intermediate **2** agrees with its stability (relative to **1**) and also with the observed small shielding of the carbonyl carbon[9] together with a displacement to higher frequencies of the neighbor methyl protons. Benzyl cations like **2** have been shown to have relatively long lifetimes since the phenyl ring stabilizes the positive charge formed on the carbonyl carbon. They have been generated thermally and trapped in organic solvents such as acetonitrile.[10] The calculated chemical shifts (ACD/Laboratories 8.00 Release) are in good agreement with this new cross-peak.

After 1.53 min, a new cross-peak is detected in HMBC-3 which belongs to the final pyrimidine **5** (167.4−8.38, blue arrow). Its intensity increases in HMBC-4 to HMBC-6.

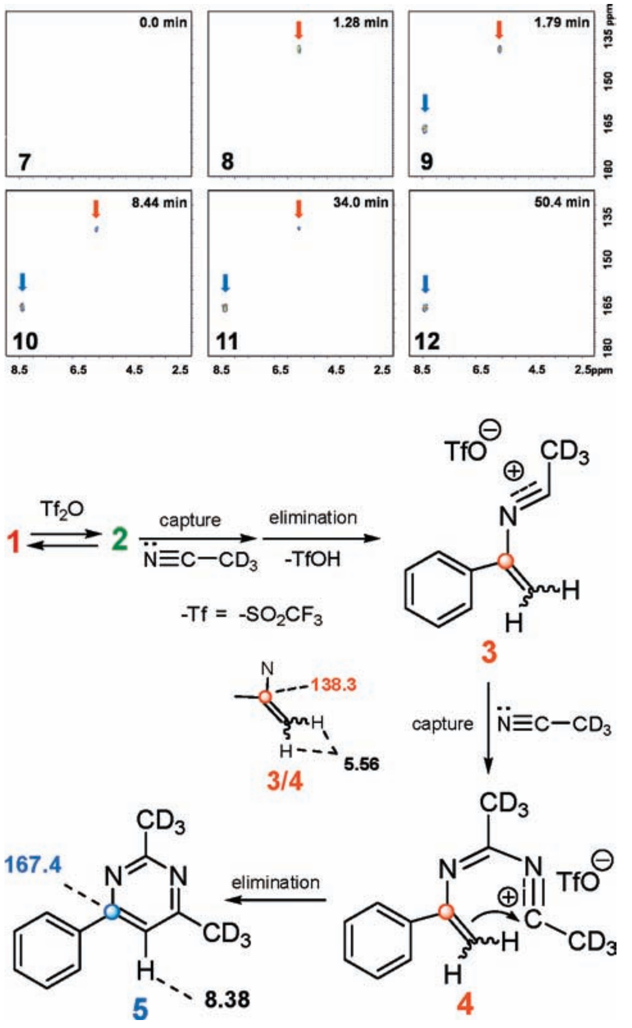

Figure 4. A series of 6 UF-HMBC experiments (7−12) obtained at increasing times along the reaction (scale is in ppm) and shifts from product **5** and participanting nitrilium intermediates **3**/**4**.

Figure 4 again shows a series of six representative 2D UF-HMBC spectra recorded corresponding to the second window studied (spectra 7−12). The ranges examined now are 180−120 ppm for ^{13}C, covering the olephinic-aromatic zone and 9−2 ppm for ^{1}H. Spectra are numbered 7−12 (referred to as HMBC-7, etc). Obviously no HMBC signals were produced by the starting ketone **1** (HMBC-7, 0.0 min). After 1.28 min a new cross-peak at 138.3−5.56 is observed in HMBC-8. We assign this cross-peak (orange arrow) to the $\underline{C}{=}CH_2$ correlation from a mixture of the olephinic nitrilium salt intermediates **3**/**4**. Their calculated chemical shifts (ACD/Laboratories 8.00 Release) are in agreement with the observed new signal.

The intensity of intermediates **3**/**4** decreases (HMBC-9 to HMBC-11) and finally disappears in HMBC-12. The intermediate character of (**3**/**4**) is shown again with their rise and fall during the reaction. The presence of pyrimidine **5** increases (HMBC-9 to HMBC-12). The presence of vinyl triflates formed by elimination of triflic acid from intermediate **2** was not detected in the UF-HMBC spectra. However

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this cannot be ruled out below the detection limit of the sequence applied. The reaction was additionally monitored by ^{1}H NMR, and the formation of a minor amount of vinyl triflates was observed. An animation of this process was made using the 219 experiments of the double set of HMBC spectra registered and the combined mechanistic information (see Supporting Information).

The variation in intensity of participant species detected along the reaction studied is clearly shown in Figure 5. Here are displayed the integrals of the cross-peaks versus time. The t lifetimes of starting ketone (**1**) and intermediates (**2** and **3**/**4**) were obtained by fitting the data points to the equation $I_{(\tau)} = I_0 \exp(-\tau/t) + I_\infty$.

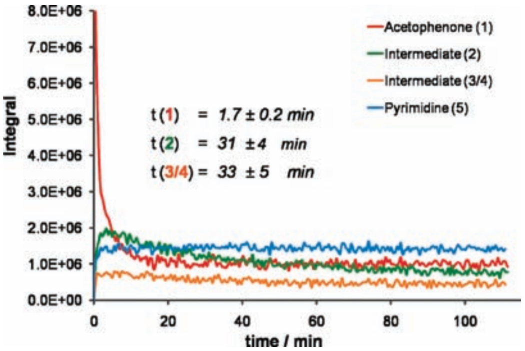

Figure 5. Averaged integrated peak intensity as a function of time for starting ketone (**1**), intermediates (**2** and **3/4**), and final pyrimidine (**5**).

Values shown in Figure 5 gave reaction rate measurements, which permits an evaluation of the reactive behavior of intermediates.

In conclusion, a two-dimensional UF-HMBC experiment is able to monitor an organic reaction and afford important structural and mechanistic information about the chemical environment and evolution of a reactive quaternary center. This technique allows the detection of different intermediate species. In the present case it has permitted the detection of an intermediate (trifluoromethanesulfonyl)carbenium ion **2** and has confirmed the presence of nitrilium salt intermediates **3**/**4**. Work is in progress to extend this methodology to studies on unlabeled carbonyl compounds and to apply the ultrafast schemes to other dynamic systems.

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Supporting Information Available: Experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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