Tetrahedron Letters 50 (2009) 1934–1938

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A closer insight into the mechanism operating in the trifluoroacetylation of pyrrole. New trifluoromethyl pyrroylmethane discovered

W. J. Peláez, M. A. Burgos Paci, G. A. Argüello *

INFIQC—Departamento de Físico Química, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Argentina

ARTICLE INFO

Article history:
Received 29 December 2008
Revised 4 February 2009
Accepted 5 February 2009
Available online 12 February 2009

Dedicated to Professor Gloria Yranzo who untimely passed away

ABSTRACT

A former studied reaction of acetylation of pyrrole was revisited and this allowed the identification of new compounds and the isolation and characterization of a very stable solid (2,2′,2″-(2,2,2-trifluoroethane-1,1,1-triyl)tris(1*H*-pyrrole)). All these materials were probably missed, buried in the black tar that characterizes the reaction. A careful and thorough selection of the reaction's conditions provided both evidence for three new compounds and a closer insight into the mechanism operating at room and lower temperatures.

The chemistry of organofluorine compounds has experienced in the last years a great deal of publications due to the numerous applications that these compounds have encountered in fields so diverse as agricultural and biological chemistry, materials science, and especially in the pharmaceutical industry.[1,2] Nevertheless, even though the introduction of fluorine atoms in the constitution of molecules usually produces significant modifications in their properties, the number of papers devoted to synthetic purposes constitutes a small fraction of the total. The availability of synthetic methods is limited to direct fluorination (both electrophilic and nucleophilic) and its use like fluorinated building blocks, as for example, α-fluoro ethers, fluoromethyl sulfides, and trifluoromethyl amines.[2,3] Today, the fluorinated moieties more commonly introduced in organic substrates are the gem-difluor (CF_2), considered an isosteric and isopolar oxygen substitution, and the CF_3-bearing subtituents.[4,5] One of the more widespread and typical reaction aimed to the incorporation of a trifluoro-methyl group is the trifluoroacetylation by trifluoroacetic anhydride (TFAA). It is an electrophilic substitution which allows introduction of a $COCF_3$ group into an activated substrate without any Friedel–Crafts catalyst,[6] and is a reaction that has been used to determine reactivities of some five-membered heteroaromatic compounds.[7] The order of reactivity for the acetylation reaction in dichloroethane is thiofene < selenophene < furan ≪ pyrrole.[8]

In the particular case of pyrrole, the reaction at room temperature is fast and continues up to the obtainment of a typical 'dark tar'[6,7] that includes known substances besides the main product, 2,2,2-trifluoro-1-(1*H*-pyrrol-2-yl) ethanone **10**, as well as new substances like 2,2′,2″-(2,2,2-trifluoroethane-1,1,1-triyl)tris(1*H*-pyrrole) **16**, that will be described, and polymeric products.[6,7] In this work, we present the new products that were missed in the dark tar of the reaction in the route to the synthesis of fluorinated porphyrins as well as a detailed theoretical study of the energetics. Relative concentrations, temperature of reaction, and order of addition of reagents were some of the parameters modified to untangle the mechanism by which the products are obtained.

The acetylation reaction was carried out in dichloro methane recently distilled at room temperature. Determination of the initial concentrations of reagents was somewhat difficult, because of high volatility and rapid hydrolysis of TFAA. Because of this, it was impossible to avoid the presence of trifluoroacetic acid TFA **2**, coming from traces of water still present in the purified solvent reacting with TFAA. Furthermore, the amount of acid increases during the reaction since it is formed as a product (Fig. 1). Nevertheless, it is essential to the reaction because it provides **3**, a powerful electrophile, as the mechanism presented in Scheme 1 (that shows only the set of reactions and species involved ending in the formation of the most abundant product) depicts.

The reaction was verified to obey third-order kinetics according to the equation $v = \kappa$ [substrate] [TFAA] [TFA **2**] as previously reported.[6] According to the described mechanism,[9] third-order kinetics would be observed through path **ABF** only if step **B** is rate controlling. As this is not so, the mechanism must proceed either through paths **CDF** or **CE**, both complying with the third-order required. Step **D** is faster than **E** (because the latter involves a concerted elimination of TFA **2** by a cyclic transition state higher in energy as calculations will show). The final step **F** should be fast because the heterolysis of the C–O bond affords a conjugated ketone and a trifluoro acetate anion which is an excellent leaving group.

Figure 2 shows that as the reaction proceeds there is an abrupt increase in the amount of **10**, which is formed in high yield. After 40 min., the other components of the mixture start to appear in

* Corresponding author. Tel.: +54 351 433 4169; fax: +54 351 433 4188.
E-mail address: gaac@mail.fcq.unc.edu.ar (G.A. Argüello).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.048

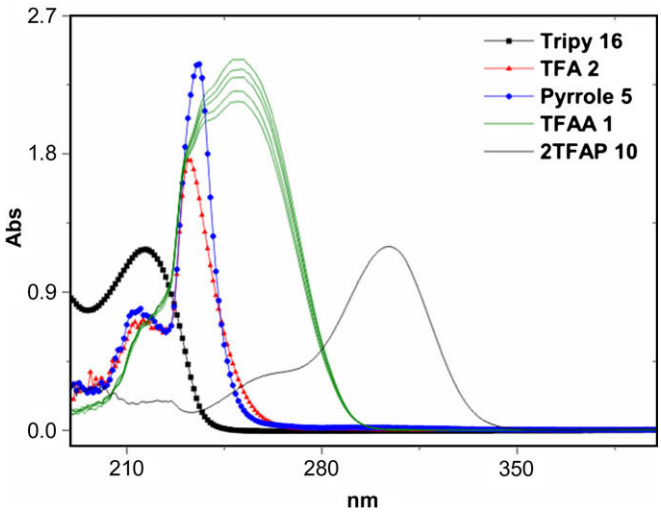


Figure 1. Hydrolysis of TFAA in the presence of traces of water in CH_2Cl_2 as well as UV absorption spectra of **2**, **5**, **10,** and **16**.

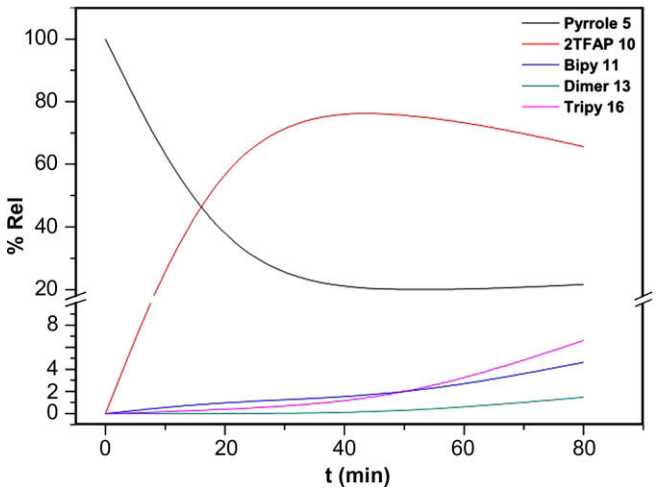


Figure 2. Trifluorocetylation of pyrrole in CH_2Cl_2 at room temperature. Quantification by CG–EM.

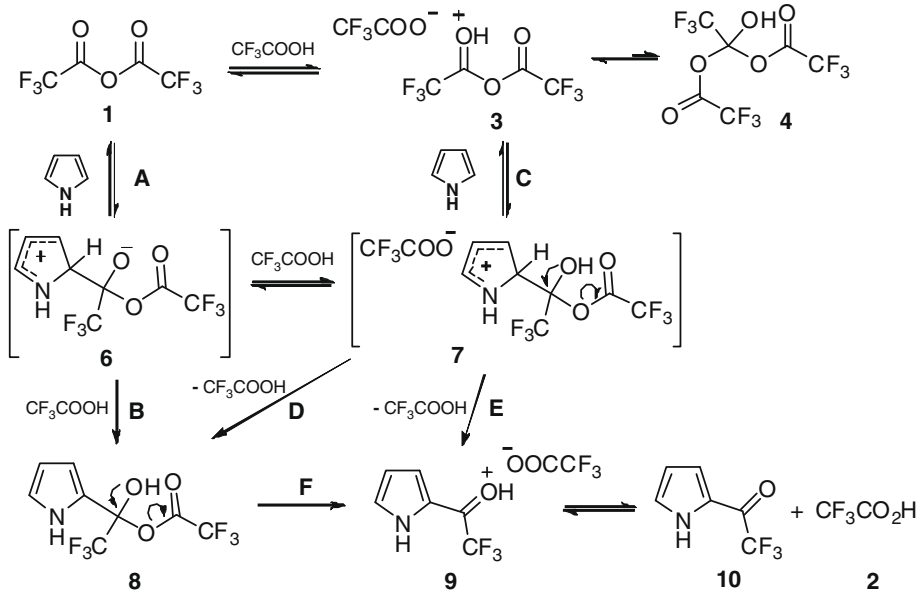
low, though steadily increasing yields in accordance with the decrease of **10** thus suggesting that **10** is the starting point to the formation of the new compounds.

The mechanism proposed in Scheme 2 shows **11** as the main intermediate that could produce **12**, **13**, **14,** and **16**. The existence of **11** has been proved by chromatographic detection through the analysis of the fragmentation pattern of its peak, though it could not be isolated. If the reaction is carried out with higher concentrations of **1** (i.e., three times more concentrated) and sufficient time is allowed for reaction to take place, **13** and **14** are obtained in the mixture, both corresponding to the two probable sites available for the acylation reaction by TFAA.

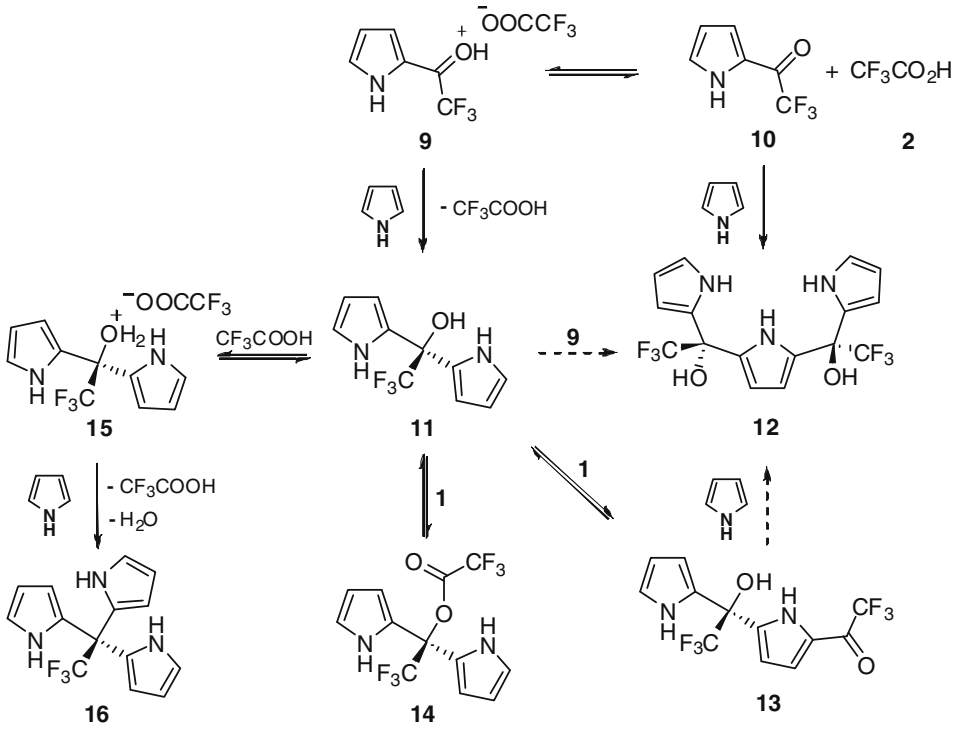
Irrespective of the change in TFAA concentration, we have always obtained 2,2′,2″-(2,2,2-trifluoroethane-1,1,1-triyl)tris(1*H*-pyrrole) **16**.

Compound **16** is a pale crystalline solid with C_3 symmetry and presents very simple ^{19}F, ^{1}H and ^{13}C NMR spectra. It has a melting point of 143–144 °C, and its UV spectrum shows a very unreactive substance under natural light with $\varepsilon_{217} = (0.2320 \pm 0.0003)\ M^{-1}\ cm^{-1}$. It shows good solubility in moderately polar solvents, very low solubility in water and no solubility in hexane. The mass spectrum reveals as base peak its molecular ion and, as expected, the main fragmentation corresponds to the loss of the CF_3 group. Analogue molecules to **16** have been synthesized having an H atom (**17**)[10] instead of the CF_3 group or phenyl (**18**)[11] and pyrazol (**19**)[12,13] instead of the pyrrole moieties (Fig. 3). This kind of interesting compounds seems to be useful as polydentate ligands to capture metallic atoms and toxic pollutants.[14,15] Recent works highlight the use of dipyrromethanes in the synthesis of meso-functionalized porphyrins.[11] The discovery of compound **16** seems to be interesting because the presence of a CF_3 group will produce a bigger change in the properties of these compounds. It is known that a fluorine substitution is a magic tool for fine-tuning the position of bioactive substances between aqueous and fatty media.[2,3] Besides, it has not been reported until date.

Numerous attempts were made to obtain this compound in higher yield, but we failed, possibly due to the number of potential



Scheme 1. Preparation of 2,2,2-trifluoro-1-(1*H*-pyrrol-2-yl)ethanone **10**.



Scheme 2. Reaction of 2,2,2-trifluoro-1-(1*H*-pyrrol-2-yl)ethanone in presence of pyrrole, TFA **2,** and TFAA.

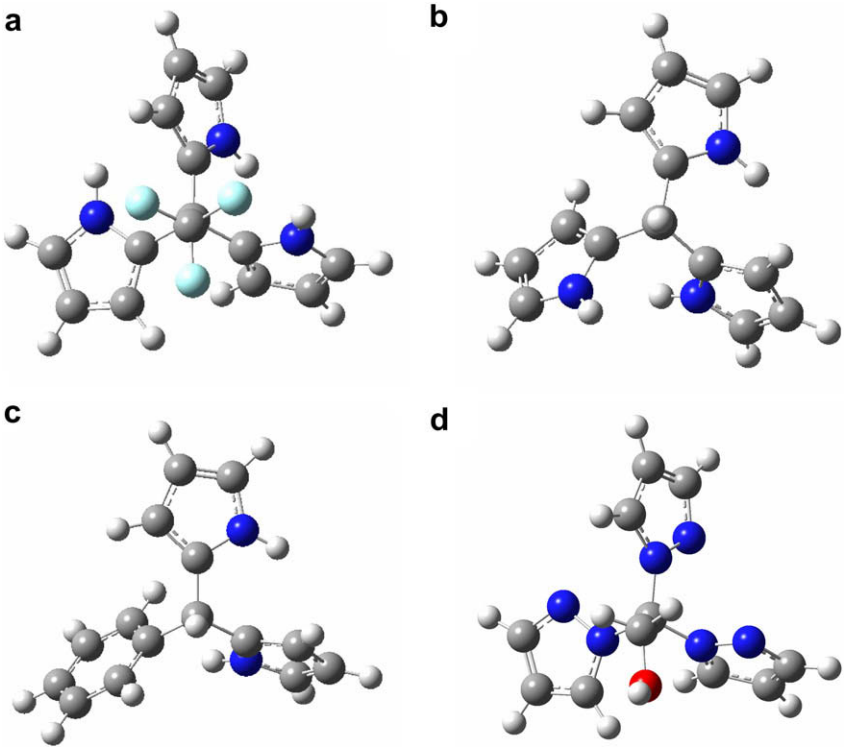


Figure 3. Top view of (a) trifluoro tripyrromethane **16**, (b) tripyrromethane **17**, (c) phenyl bipyrromethane **18,** and (d) CH_2OH trispyrazomethano **19**.

reaction channels that open for the intermediate **11**. As stated before, **11** could not be isolated from the crude of the reaction and so, subsequent reaction with the highly reactive pyrrole, led to polymerization reactions that generated 'Pyrrol-red'.[8]

We have also proved, in independent reactions with mass spectrometry as detection method, that when **10** reacts with **5** in a simple mixture at room temperature, **12** is obtained in 10.3% yield. This path is portrayed in Scheme 2 as well as two other possible reaction paths, specifically the attack of the protonated 2TFAP **9** on **11** and the attack of pyrrole on the carbonylic carbon atom from **13**. Neither of these channels can be a priori discarded because the analysis of the crude of reaction

by GC/MS precludes the introduction of low volatility compounds as **12.**

Moreover, it was proved in separate experiments, that it is not possible to directly obtain **13** from **10**; that is, the dimerization does not take place, probably due to the deactivation of 2TFAP **10** in the electrophilic aromatic substitution reaction.

Steps **D** and **E** of Scheme 1 were studied by quantum chemistry calculations using the GAUSSIAN 03 program package[16] at the B3LYP/6-311G level. Transition state theory was used to evaluate the energy of the different channels (Scheme 3). The transition states were characterized by the presence of one negative frequency and the internal reactions coordinate (IRC) method was applied to verify that the correct states were connected. The calculations were run in the gas phase since the polarity of the solvent used in the experiments is rather low.

The step involving the transition state $\mathbf{TS_D}$ corresponds to the abstraction by the acetate of the α′-hydrogen to give the intermediate **8** that immediately dissociates to form **9** ⇄ **10**. An analysis of the potential energy surface indicates that the abstraction is coordinated with the rupture of the linkage C_α–O_β and thus, the intermediate **8** should not accumulate. In this way, **9** ⇄ **10** is generated straightforwardly.

It was found that **10** can also form an aggregate with two molecules of TFA **2** stabilized by the formation of three hydrogen bridges as presented in Figure 4. Except for the axial fluorides of the CF_3 groups the structure is planar and highly symmetric, and could be assigned as belonging to the C_s group. Its geometrical parameters are given as SI.

Step **E** corresponds to the intramolecular abstraction of the α′-hydrogen atom by either of the two oxygens of the hemiacetal moiety. If the abstraction was through the β-oxygen, it would give a four-membered transition state, $\mathbf{TS4_E}$; but if it was through the δ-oxygen, a six-membered transition state $\mathbf{TS6_E}$ would be expected. The results show that $\mathbf{TS6_E}$ is 17.8 kcal mol^{-1} more stable than $\mathbf{TS4_E}$. Nevertheless, comparing the energetic of channels **D** and **E**, it results that channel **D** is favored since there is almost no activation energy.

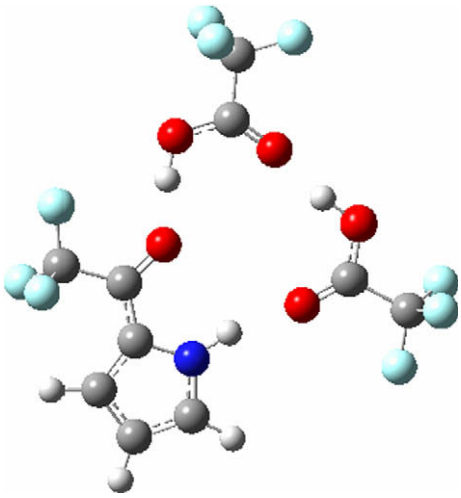
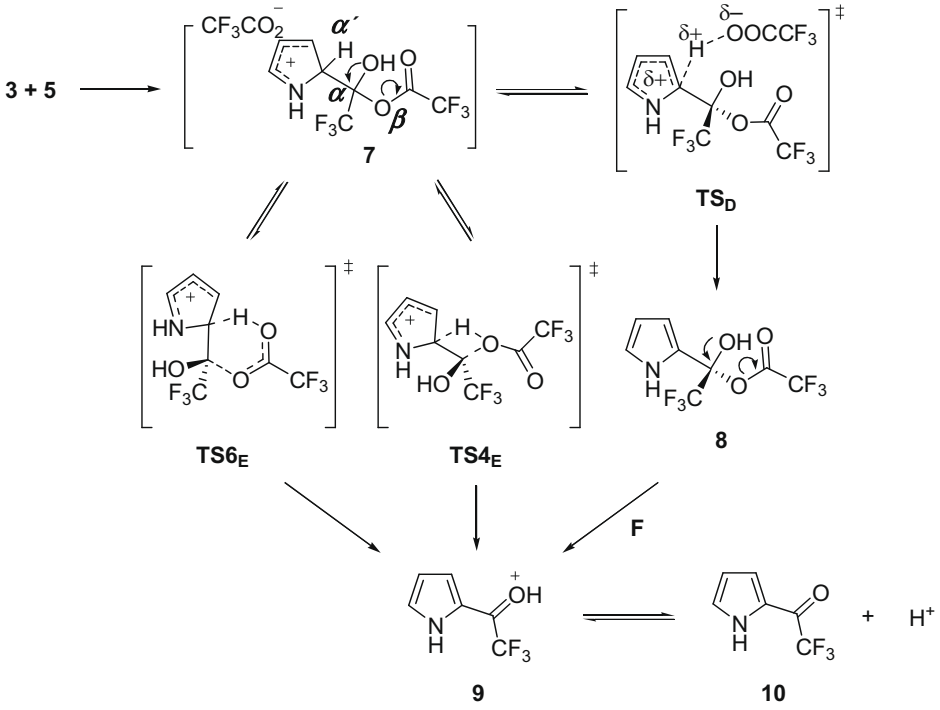


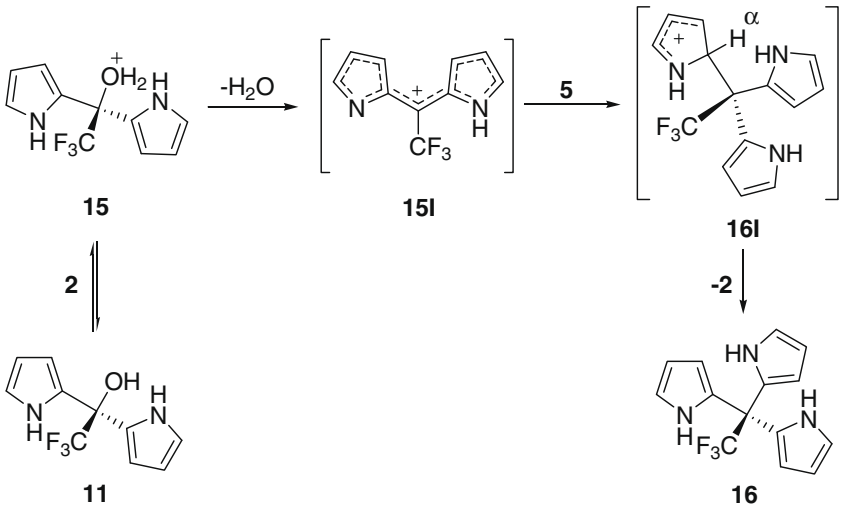
Figure 4. Aggregate obtained as the product of TS_D.

In order to get some insights into the mechanism connecting **11** and **16,** DFT calculations at the level already mentioned were run. We suggest that the—OH group in **11** could take a proton from the TFA **2**, forming the cation **15** which will eliminate a water molecule spontaneously and form the intermediate cation **15I**, susceptible to the addition of a pyrrole molecule to give the σ-complex **16I** shown in Scheme 4.

The reaction of **15I** and pyrrole is 0.48 kcal mol^{-1} endothermic, with activation energy of 7.1 kcal mol^{-1}. The endothermicity of this reaction can be attributable to the loss of resonance in the pyrrole fragment attacking the cation. The α proton of **16I** should be abstracted by acetate to form **16** and TFA **2** through a transition state similar to $\mathbf{TS_D}$, in a reaction which is 188 kcal mol^{-1} exothermic. The high exothermicity informed accounts for the coulombic factor of the neutralization and the resonance energy acquired by the system.



Scheme 3. Transition states for steps **D** and **E**.



Scheme 4. Reaction of formation of **16**.

This work has shown that new compounds could be obtained with some changes in the conditions of an old reaction. This opens new ways (since the yields so far obtained are relatively low, renewed efforts will be put in their study) to synthesize compounds bearing fluorinated groups.

Acknowledgments

Financial support from CONICET and SeCyT-UNC is gratefully acknowledged. W.J.P. wants to thank CONICET for the fellowship granted.

Supplementary data

Synthetic procedures, characterization and calculated data from GAUSSIAN03 of compound **10**, **11**, **12**, **13**, **14,** and **16** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.048.

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