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Mechanistic Investigations of the Formation of TTF Derivatives via the Phosphonate Way

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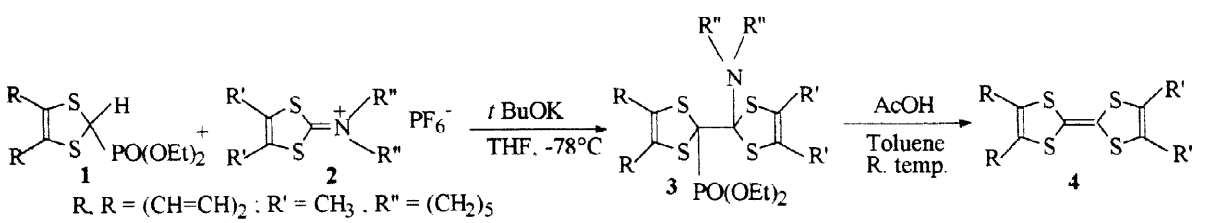
Abstract: We studied the influence of acetic acid concentration on the deamination and dephosphonylation of the adduct resulting of the nucleophilic reaction between adequate α-metalated phosphonate and imminium salt, to enhance the yield of such reactions in order to access efficiently a lot of unsymmetrical TTF derivatives. A mechanism is proposed for the formation of TTF, including steps, i_1 to i_7. The potential concurrent formation of phosphonate 1 and other by-products is also discussed.

Among the pathways described in the literature[1,2] to access unsymmetrically substituted TTF derivatives the "phosphonate way" seems to be an efficient method (scheme 1)[2]. Unfortunately, low yields (20-50 %) and restricted scope of this process[2] are still observed in most cases and remain the two major limitations to be overcome.



Scheme 1

In this study, we took as a model (scheme 1) the synthesis of TTF **4**, a known compound obtained in 30% yield by another way[3]. We now report the first results of our investigations aiming to improve its synthesis through a better understanding of the mechanisms involved in this kind of reaction. The starting materials are the diethyl 2-[4,5-benzo-1,3-dithiolyl] phosphonate **1**,[4] and the 4,5-dimethyl-1,3-dithiole-2-yliden piperidinium hexafluorophosphate **2**,[5] prepared and identified as indicated in the literature. The investigated reaction (scheme 1) was monitored by ^{31}P-nmr spectroscopy. The first step involves the deprotonation of phosphonate **1** by *t*-BuOK, giving rise quantitatively to the corresponding phosphonylated carbanion **1'** characterized by the appearance of a singlet at 8.95 ppm. The carbanion was allowed to react with imminium salt **2** to quantitatively provide adduct **3** as confirmed by the appearance of only one single signal at 16.68 ppm clearly differentiated

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from the signal at 16.24 ppm, corresponding to the coinjected ester **1**. The air sensitive compound **3** was isolated by filtration under nitrogen, and characterized from its spectroscopic data and particularly by ^{1}H-nmr with the deshielding of the protons of its piperidinyl group in comparison with compound **2**. Furthermore, as shown by ^{31}P-nmr, at room temperature, no reverse reaction of **3** into **1** was observed, except after heating the adduct **3** during 52h at 65°C or 4h30 at 110°C which induces the formation of phosphonate **1** in 40 or 100% yield respectively. These results clearly showed that the first step of this TTF **4** synthesis is not the limiting phase of the reaction at room temperature, adduct **3** being quantitatively obtained.

In general[2], deamination and dephosphonylation of type **3** adduct to obtain the TTF derivative were performed, by adding acetic acid to this adduct at room temperature until the expected compound precipitated. This method was not satisfactory and the TTF species was isolated in low yield. In view to improve the yield, using the same protocol[6], an understanding of the mechanism of the AcOH action on the adduct **3**, and consequently on the phosphorus and nitrogen groups elimination, seemed to be necessary. In our study, the initial concentration of the starting materials and of the quantitatively formed adduct being [**1**] = [**2**] = [**3**] = 57 10^{-3} mol / l, we found a relationship between the yield of the TTF compound **4** obtained (table) and the ratio ρ = [AcOH] / [**3**]. In all examined cases, with different values of ρ, the progress of the corresponding reactions was studied by ^{31}P- and ^{1}H-nmr spectroscopy. The resulting compounds were identified, by addition of authentic samples to the nmr-medium. Using dibenzyl ether (DBE) as an internal reference, the data of the qualitative and quantitative analysis of the corresponding reaction mixtures (after the disappearance of the signal of **3** and evaporation of the solvent together with the excess of AcOH) are indicated in the **table**.

The best result was obtained when ρ = 10, therefore an excess of AcOH seems to be necessary. Indeed when freshly redistilled anhydrous AcOH was used, with ρ = 1, the ^{31}P-nmr spectra of the crude reaction mixture indicated the transformation of adduct **3** into only one phosphorus compound, the phosphonate **1** (15% after 2h, and complete after 48h). The presence of compound **1** as well as the absence of TTF **4**, were corroborated by the ^{1}H-nmr spectra, where there also appeared the signals of the imminium salt **2** of the piperidinium salt **5** and of an unidentified piperidinium derivative[7]. Under these conditions most of the adduct **3** undergoes a reverse transformation into the starting materials **1**, **2** and some amount of **5** and **2'**. The reaction pathway (scheme 2) seems to be successively: $ii_{1\text{-}2}$ to the extent of 70%, and for the side products $i_{1\text{-}4}$,. In step i_4, we assume that the small amount of water introduced in the final work up of the reaction plays a role. This was confirmed when commercial glacial AcOH was used, once again with ρ = 1; when we observed nearly the same results: presence of phosphonate **1**, of piperidinium salt **5** to a greater extent, and of thiocarbonate **7** and the absence of imminium salt **2**. The reaction seems to follow the same pathway as in the previous case with a preference for the route $i_{1\text{-}4}$ over way $ii_{1\text{-}2}$. The degree of formation of the phosphonate **1** decreases from 100 to 7 % when the ratio ρ increases from 1 to 10. Meanwhile the yields of TTF **4** and also of diethylphosphate **9** increase.

For example, when the reaction was run with 10 equivalents of AcOH, ^{31}P-nmr analysis of the reaction mixture (**table**, entry 4) indicated that diethyl phosphate **9** was the most important phosphorus compound formed. Its signal at -1.03 ppm (92%) was assigned by addition of an authentic sample to the nmr-mixture. It was accompanied by two other signals at 16.24 ppm corresponding to the phosphonate **1** (7%) and at -8.69 ppm (8%) not assigned, that disappeared after evaporation of the solvents (toluene and AcOH). Then the reaction mixture was quantitatively analyzed by ^{1}H-nmr spectroscopy, the presence of phosphate **9** and phosphonate **1** were confirmed without detection of any other phosphorus compound. The signal at - 8.69 ppm in the ^{31}P-nmr spectrum, could reveal the presence of a labile intermediate, perhaps the mixed anhydride **8**, which is split, during the final work-up. Also found, were the characteristic signals of compounds **4**, **6**, **5** and **7**, as verified by addition of each corresponding authentic sample and by GC-Mass analysis of the mixture of compounds **4**, **6**, and **7**.

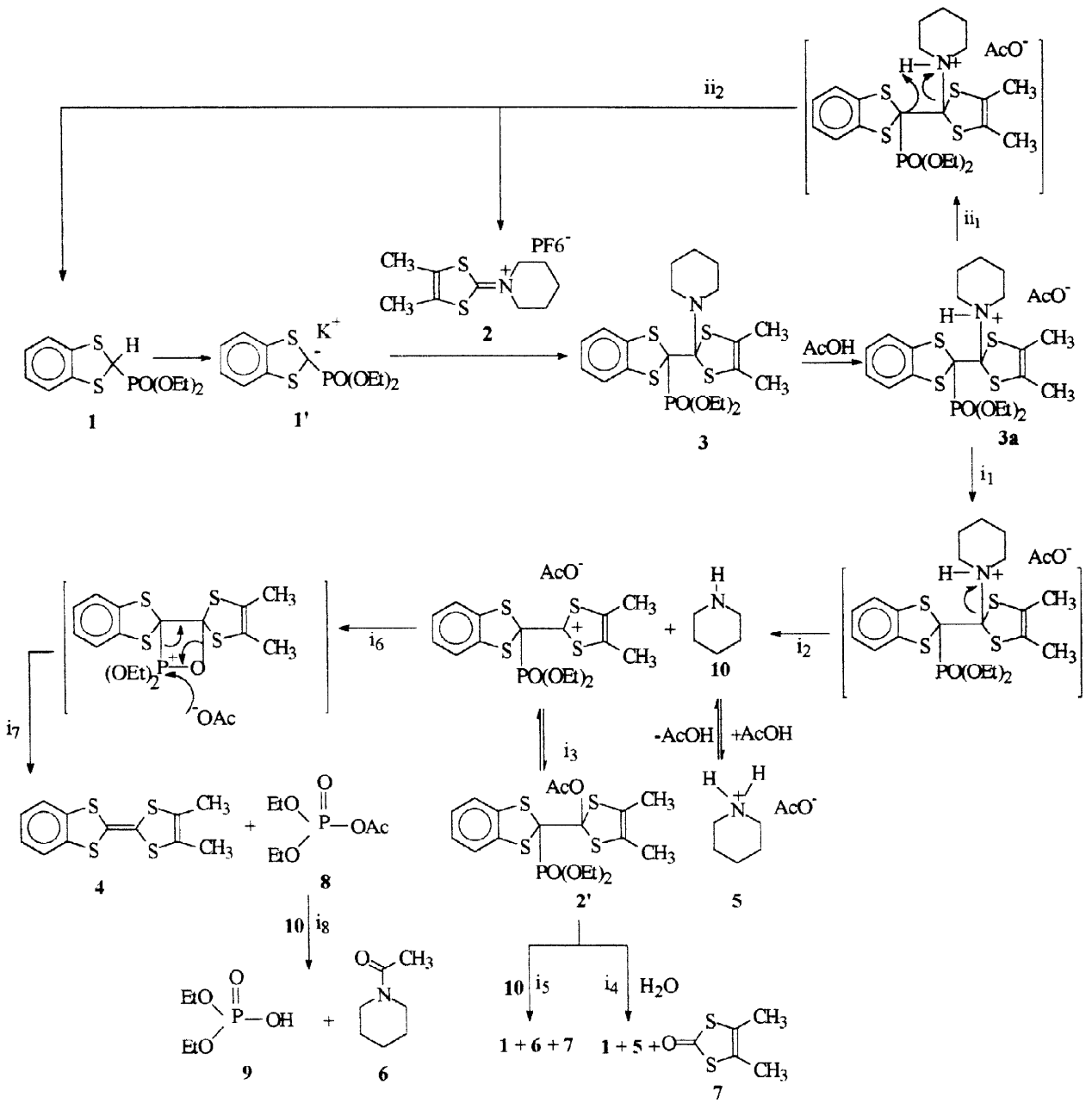
Table - Synthesis of TTF **4** by reaction of AcOH on adduct **3** (scheme 1, 2) depending on ρ = [AcOH] / [**3**]: yield (Yd) and formation degree (Fd) obtained from ^{1}H and ^{31}P-nmr analysis

Entry	ρ	Yd (%)[d]	Fd (%)	Fd (%)[f]						
		4	**1**[e]	**4**	**1**	**9**	**7**	**6**	**5**	**2**	**2'**[g]
1[a,b]	1	0	100	0	100	0	0	0	15	70	15
1[a,c]	1	0	100	0	100	0	15	0	64		36
2[a,c]	3	15	28	36	24	76	7	61	18		
3[a,c]	7	50	19	72	19	81	8	58	22		
4[a,c]	10	53	7	77	8	92	7	42	25		
5[h,b]	10	78	0	86	0	100	4	72	20		
6[h,b,i]	10	80	0	90	0	100		69	36		

[a] [**3**] = 57 10^{-3} mol / l; [b] freshly anhydrous distilled AcOH was used; [c] freshly redistilled commercial glacial AcOH; [d] yield of isolated pure compound; [e] normalized ratio from the other signals based on ^{31}P-nmr spectra; [f] degree of formation calculated from ^{1}H-nmr spectra (DBE was used as internal reference); [g] unidentified piperidine derivative (ref. 7); [h] [**3**] = 229.66 10^{-3} mol / l; [i] one pot reaction from the starting material **1** ([**1**] = 229.66 10^{-3} mol / l); without isolation of adduct **3**.

As indicated in scheme 2, we can conclude that the reaction pathway to TTF **4** formation is likely to be $i_{1\text{-}7}$ and to phosphonate **1** formation to be either $ii_{1\text{-}2}$, $i_{1\text{-}4}$, or $i_{1\text{-}5}$ (together in the last two cases with the N-acetyl piperidine **6** or with the piperidinium acetate **5** respectively). The difference in polarity of the medium due to the presence of AcOH in a large or small amount, could explain the behaviour of adduct **3** and therefore the results observed. We also noted that using the same protocol[6] with ρ = 10, an enhancement of the concentration of [**1**] = [**3**] to 229.66 10^{-3} mol / l increases the yield of TTF **4** (Table, entry 5). Moreover when the reaction was carried out "*one pot*" in the same solvant (THF) from phosphonate **1** ([**1**] = 229.66 10^{-3} mol / l) to TTF **4**, this last compound was obtained with 80% yield **4** (Table, entry 6).

We are now studying the extension and the efficiency of this protocol, to other known and novel unsymmetrically substituted TTF.



Scheme 2

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6. -The protocol[2a] implies: the formation at - 78°C in THF solution of the adduct **3**, its isolation in solution, by filtration; a change of solvant: toluene instead of THF; and addition of AcOH at room temperature.

7. The spectroscopic data of the unidentified compound are: ^{1}H-NMR δ ppm: 3.56 (4H, m); 1.5-1.8 (6H, m); GC / MS: 215, 173, 112, 69, 43