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On the regioselectivity of the PIFA-mediated *bis*(trifluoroacetylation) of styrene type compounds.

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Abstract.

The addition of the hypervalent iodine reagent PIFA [phenyliodine(III) *bis*(trifluoroacetate)] to a series of styrene type compounds results in the *bis*(trifluoroacetylation) of the double bond as two possible 1,2- and 1,1-regioisomers. We found that 1,1-regioisomers resulted to be unstable during chromatographic purification yielding the related arylacetaldehydes. In this communication we show our efforts to explore the regioselectivity of this reaction, and to rationalize the results with respect to the electronic nature of the corresponding aryl ring through alternative mechanistic pathways.

Keywords: hypervalent iodine, styrenes, PIFA, phenonium ions

1. Introduction.

Among all possible ways to perform the *cis*-dihydroxylation reaction of olefins, the centennial¹ use of OsO₄ has gained an enormous popularity over the years for its reliability and, more recently, for its evolution into an effective asymmetric strategy for the preparation of enantiomerically pure vicinal diols when used in the presence of chiral ligands.² Although used under substoichiometric conditions, the toxicity of the osmium reagents has led to the exploration of novel systems with the same synthetic purpose. In particular, and among others, the use of hypervalent iodine reagents, such as propyliodine(III) *bis*(trifluoroacetate)³ or iodine(III) *tris*(trifluoroacetate),⁴ performs the *bis*(trifluoroacetylation) of the CC double bond although with limited success. More recently,⁵ Çelik and Balci have demonstrated the efficiency of PIFA [phenyliodine(III) *bis*(trifluoroacetate)] in the

direct transformation of acyclic as well as cyclic alkenes into 1,2- and/or 1,3-*bis*(trifluoroacetoxy) derivatives.⁶ Particularly, under such conditions, styrene was transformed into 1-phenyl-1,2-ethanediol in a 90% yield after ammonolysis of the *bis*(trifluoroacetoxy) intermediate generated.

At the same time this work was being published, we were involved in a related long lasting project on the search for novel applications of PIFA in organic synthesis, and more precisely on the intramolecular PIFA-mediated olefin amidation of conveniently substituted styrene type substrates as a new entrance to the synthesis of quinoline and isoindoline derivatives.⁷ In this particular context, we expect that the high electrophility of the iodine center in PIFA, as well as the lability of the trifluoroester groups that are eventually transferred to the olefinic substrates, might have important consequences in the outcome of the reaction. Thus, in this communication we report some preliminary results on the action of PIFA on such kind of derivatives to show that the regioselectivity of the reaction (1,1- versus 1,2-diester formation) depends mostly on the activation of the aryl ring.

2. Results and discussion.

As mentioned, styrene (**1a**) affords 1-phenyl-1,2-*bis*(trifluoroacetoxy)ethane (**2a**) in the presence of PIFA in almost quantitative yield when the reaction is carried out in CH₂Cl₂ as solvent. Considering the importance of the 1-aryl-1,2-ethanediol skeleton in organic synthesis,⁸ it is surprising that the study on the action of PIFA has not been extended to other members of the family of styrene compounds. Alerted by the absence of research in this area, and continuing with our interest in discovering novel applications of PIFA in organic synthesis,⁹ we started our study by exploring the action of this iodine (III) reagent on a series of commercially available styrenes **1a–f** (see Chart 1).

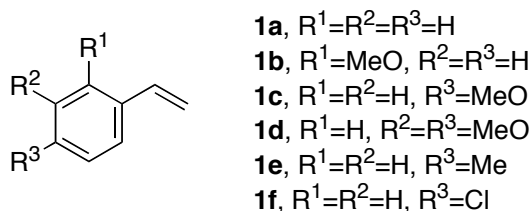


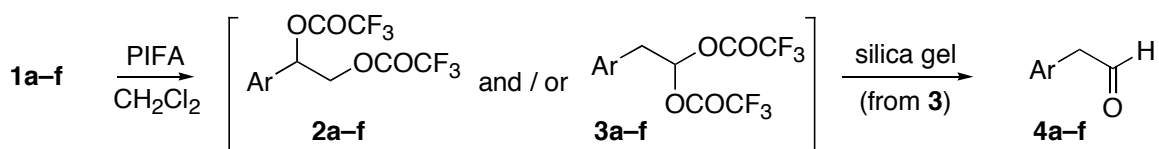
Chart 1.

Styrenes **1a** and **1b** were selected to optimize the reaction conditions. Our preliminary observations led us to conclude that the nature of the aryl ring, and also the dilution of the reaction at some extent, had a critical effect on the regioselectivity of the process. Thus, while treatment of styrene **1a** with PIFA (0.3–0.5 M in CH₂Cl₂ at room temperature)¹⁰ rendered exclusively the 1,2-diester **2a** in 4 hours,

styrene **1b** afforded the related 1,1-diester **3b** with complete regioselectivity in few minutes. It has to be mentioned that, unlike **2a**, diester **3b** happened to be unstable during column chromatography resulting in the formation of 2-(2-methoxyphenyl)acetaldehyde (**4b**). Thus, in order to optimize the work up, and prior to its purification, the non-isolated diester **3b** was treated with silica gel and the stirring was continued overnight to afford aldehyde **4b** in 74% yield.¹¹ This completely regioselective one-pot transformation can be considered as a metal-free alternative to the Wacker process for which the highly selective formation of aldehydes through catalytic oxidation of styrene-type compounds without CC double bond cleavage remains a challenge.^{12,13}

Therefore, in order to gain more information about the insights of this transformation, the behavior of a series of styrenes **1c–f** with different activation pattern with the iodine (III) reagent was studied. From the information summarized in Table 1, it can be deduced that 1,1-addition to the double bond dominates when starting from activated substrates (**1b–e**), and contrarily, non-activated styrenes tend to afford the 1,2 adducts **2a,f**.¹⁴ Besides, in some cases (entries 2,3,5,6), the generation of the corresponding arylacetaldehydes **4** is detected at some extent in the reaction mixture even before the addition of silica gel.

Table 1. Selected synthetic and spectroscopic information for the action of PIFA on styrenes **1a–f**.



Entry	Styrene ^{a)}	2 (%)	Ratio 2/3/4 ^{b)}	3 ($\delta_{\text{H-1}}$, $\delta_{\text{H-2}}$, $J_{\text{H-1/H-2}}$)	4 (%) ^{c)}
1	1a	82	100/0/0	-	-
2	1b	0	0/88/12	7.22 ppm, 3.31 ppm, 5.7 Hz	74
3	1c	0	0/75/25	7.04 ppm, 3.24 ppm, 5.9 Hz	85
7	1d	0	0/100/0	7.04 ppm, 3.23 ppm, 5.7 Hz	39
5	1e	traces	5/73/22	7.04 ppm, 3.25 ppm, 6.0 Hz	69
6	1f	87 ^{ref. 14}	95/0/5	-	traces

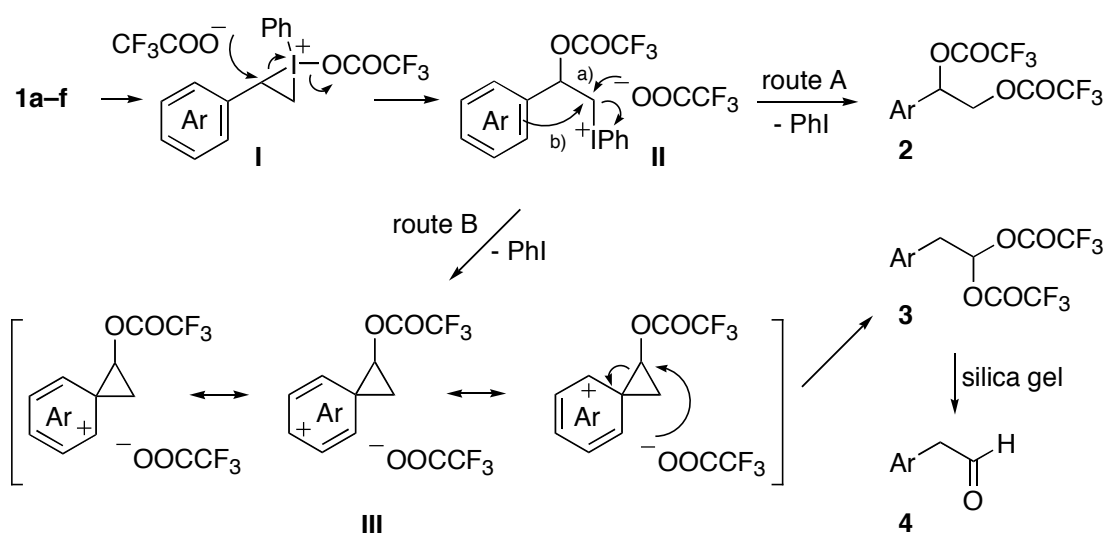
a) Styrene/PIFA (1/1.2), 0.40 M in CH_2Cl_2 at room temperature.

b) Selectivity was determined from the ^1H NMR spectra of the crude mixture before addition of silica gel.

c) Arylacetaldehydes **4** are extremely unstable, and they were isolated as oils by column chromatography. Some of them are commercially available and others have been described previously. In any case, their spectroscopic data match literature values.¹⁵

To the view of these results, the following mechanism can be postulated (see Scheme 1). Due to its electrophilic character, the hypervalent iodine reagent reacts with the olefinic double bond in substrates

1a–f to afford the iodonium intermediates **I**, which are opened by a nucleophilic attack of the trifluoroacetate group. Final displacement of iodobenzene by a second trifluoroacetate group¹⁶ (route A) affords the 1,2-*bis*(trifluoroacetates) **2**. Alternatively, activated aryl rings (in substrates **1b–e**)¹⁷ can proceed as a second nucleophilic competitor giving rise, in these cases, to intermediates **III** following route B. These phenonium intermediates recover their aromaticity by reacting with a trifluoroacetate group at their most activated benzylic position furnishing the 1,1-*bis*(trifluoroacetates) **3**, which, on standing on silica gel, are transformed into the arylacetaldehydes of type **4**. It has to be mentioned that the generation of phenonium ion intermediates had already been postulated¹⁸ and their existence demonstrated,¹⁹ even under the action of hypervalent iodine species.²⁰



Scheme 1. Proposed alternative mechanisms for the action of PIFA on styrenes **1a–f**.

3. Conclusions

The behavior of a series of styrenes in the presence of PIFA has been studied to conclude that non-activated substrates suffer 1,2-addition of trifluoroacetate groups across the olefinic double bond, whilst a related 1,1-addition dominates the reactivity on activated ones. A mechanistic description of this reaction includes the generation of a phenonium ion with concomitant 1,2-migration of the aryl ring. Taking advantage of the lability of such *gem*-diesters, they can be transformed into the corresponding carbonyl compounds on standing with silica gel. This unprecedented procedure for the direct generation of arylacetaldehydes from 1-arylethenes can be considered a competitive metal-free alternative to the Wacker reaction.

4. Experimental Section.

General procedure for the synthesis of bis(trifluoroacetates) 2. To a magnetically stirred solution of the corresponding styrene (1 mmol) in CH₂Cl₂ (5 mL), PIFA (1.2 mmol) was added in one portion. Then, the stirring continued at room temperature until total consumption of the starting material. After removal of the solvent, the residue was chromatographed on silica gel eluting with hexane/ethyl acetate (80:20) to give the 1,2-diester as colorless oils.

General procedure for the synthesis of carbonyl compounds 4. To a magnetically stirred solution of the corresponding styrene (1 mmol) in CH₂Cl₂ (3 mL), PIFA (1.2 mmol) was added at once. After 15 minutes, silica gel was added and the stirring continued overnight. The mixture was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (90:10) to give the related carbonyl compounds 4 as yellowish oils.

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10. At higher dilution, the reaction time was prolonged excessively.
11. Diesters **3b–e** were identified by the aid of selective TOCSY experiments from the crude reaction prior to the addition of silica gel. See selected information in Table 1.
12. (a) The oxidation of alkenes to carbonyl compounds catalyzed by palladium (II) salts (known as the Wacker reaction) normally proceeds with Markovnikov regioselectivity. For a novel anti-Markovnikov regioselectivity (leading to aldehydes from terminal olefins) in the Wacker reaction of styrenes, see: Wright, J. A.; Gaunt, M. J.; Spencer, J. B. *Chem. Eur. J.* **2005**, 12, 949–955, and more recently, Muzart, J. *Tetrahedron* **2007**, 63, 7505–7521. (b) The catalytic anti-Markonikov hydration of terminal alkynes to aldehydes has been also described. See: Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, 126, 12232–12233.
13. Phenylacetaldehyde (**4a**) is a common byproduct also obtained directly during the oxidation of styrene into styrene oxide by a number of reaction conditions. For a recent example, see: Zhang, J. –L.; Che, C. –M. *Chem. Eur. J.* **2005**, 11, 3899–3914. Additionally, it has been shown that styrene oxides suffer rearrangement of the epoxide ring with InCl₃ to afford the corresponding arylacetaldehydes in good yields. See: Ranu, B. C.; Jana, U. *J. Org. Chem.* **1998**, 63, 8212–8216.
14. Diester **2f** resulted to be very unstable on silica gel. Therefore, it was identified from the crude ¹H NMR by the distinctive A₂M system of its aliphatic protons [selected absorptions: 6.20 (dd, J=8.3, 3.6, 1H, H-1); 4.69 (dd, J=12.2, 8.3, 1H, H-2a); 4.59 (dd, J=12.2, 3.6, 1H, H-2b)], and by its transformation into the corresponding known 1-(*p*-chlorophenyl)-1,2-ethanediol (Tsujigami, T.; Sugai, T.; Ohta, H. *Tetrahedron: Asymmetry* **2001**, 12, 2543–2549) using NaBH₄ in MeOH. The yield given in Table 1 is referred to the combined steps.

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