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Chemistry in Water - Part VI
Catalytic Isomerization and Stereochemistry of Reduction of Acetylenics Mediated by Water-Soluble Phosphines

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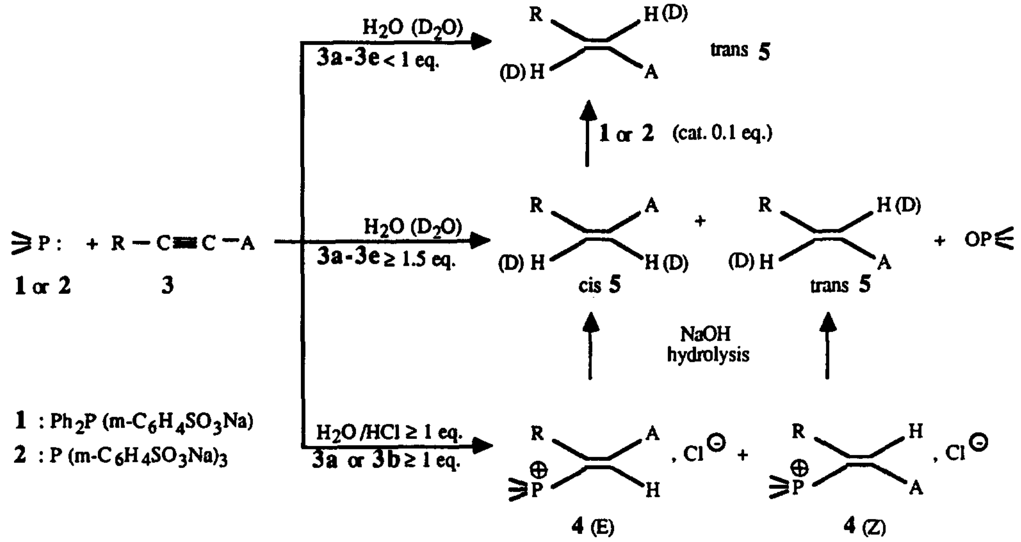
Abstract : *Reaction of water-soluble phosphines with disubstituted electrodeficient alkynes in H_2O (D_2O) gives rise either to mixtures of cis and trans (dideuterated) olefins or specifically to trans (dideuterated) olefins, by simple control of the phosphine amount. A cis-trans olefin isomerization catalyzed by sulfonated phosphines occurs in water and allows the obtention of specifically trans disubstituted alkenes from the corresponding cis isomers.*

Recently, emphasis has been put on organic chemistry in water to take advantage of the specific properties of this unusual solvent such as the so-called hydrophobic effect which modifies the kinetics and the stereoselectivities of organic reactions like for example cycloadditions.[1] In this field, we have studied the reactivity of water-soluble phosphines, monosulfonated and trisulfonated triphenylphosphine TPPMS **1** and TPPTS **2**, towards unsaturated organic molecules such as electrodeficient alkenes or alkynes.[2] In these nucleophilic additions, water acts as an acido-basic reagent which shifts equilibria towards the quantitative formation of alkyl- or vinyl-phosphonium salts.[2] The reaction of TPPMS **1** or TPPTS **2** with disubstituted alkynes **3a-e** gives rise to the corresponding trans-disubtituted alkenes **5a-e** via hydrolysis of the intermediate vinylphosphonium salts **4**, in one step when the reaction is performed in neutral medium or in two steps after addition of base on the isolated vinylphosphonium salts **4a-c** when the reaction is performed in the presence of at least one equivalent HCl [2a,3] (Scheme). Specifically mono- and di-deuterated olefins have thus been obtained by sequential use of H_2O and D_2O.[2a]

In this paper, we demonstrate that aqueous solutions of sulfonated phosphines **1** or **2** efficiently catalyze the cis → trans isomerization of disubstituted electrodeficient alkenes. The obtention of specifically trans-disubstituted olefins by reaction of water-soluble phosphines with the corresponding alkynes involves in fact two steps : (i) a stereospecific hydrolysis of E and Z vinylphosphonium salts leading to a mixture of cis and trans olefins and (ii) a catalytic cis → trans isomerization of the resulting olefins by a slight excess of phosphine.

Thus, mixtures of Z and E vinylphosphonium salts **4a** (Z/E = 70/30) and **4b** (Z/E = 60/40) have been prepared in aqueous solution from the reaction of TPPMS **1** with **3a** and **3b** in the presence of stoechiometric amounts of HCl.[4] Upon addition of sodium hydroxide, mixtures of cis and trans olefins **5a** and **5b**, with relative cis/trans ratio [5] 30/70 for **5a** and 40/60 for **5b**, are quantitatively obtained thus demonstrating the stereospecificity of the hydrolysis [6] (Scheme). When the reaction of TPPMS **1** is performed in neutral medium with an excess of acetylenic compounds **3a-e**, hydrolysis occurs *in situ* and gives rise to the expected mixture of cis and trans olefins [5] (Scheme, Table).

Nevertheless, as already described, [2a] the trans olefin is the unique product when the reaction of **3a-e** with TPPMS **1** is carried out with a slight excess (0.01 to 0.1 eq.) of phosphine. GC analysis of the evolution of the cis-trans isomeric ratio of **5a**, resulting from hydrolysis of the vinylphosphonium salts **4a** in water [4], in the presence of a slight excess (0.1 eq.) of **1**, shows that **5a** cis is readily and quantitatively isomerized into **5a** trans by the phosphine in excess.[7]

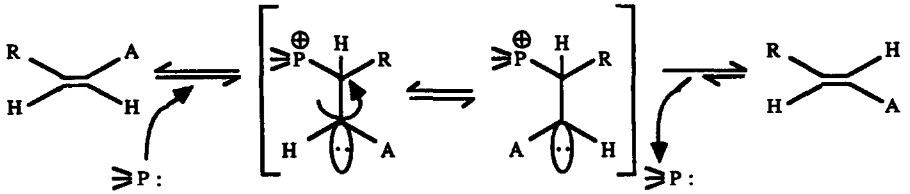


a : R = Ph, A = COMe ; b : R = Ph, A = CHO ; c : R = Ph, A = CO_2H ; d : R = A = CO_2Me ; e : R = A = $CO_2CH_2CH(Et)(Bu)$.

The cis → trans isomerization of disubstituted olefins catalyzed by the water-soluble phosphine is unambigously demonstrated for dimethyl maleate, **5d** cis, which is quantitatively transformed into fumarate, **5d** trans, after stirring for 2 hours at room temperature with an aqueous neutral solution of **1** (catalytic amount : 0.1 or 0.01 eq.). The phosphine **1** remains unchanged in the aqueous phase [7] and can be easily reused for further isomerizations after separation of the organic product. The same catalytic isomerization [8] is observed (i) for other disubstituted alkenes **5** and (ii) in the presence of catalytic amounts of trisulfonated phosphine **2**. Nevertheless **2** is slightly less efficient than **1** since its progressive oxidation limits the number of recyclings.

This cis → trans isomerization catalyzed by water-soluble phosphines **1** or **2** does not involve a protonation step since the isomerization of maleate **5d** in the presence of D_2O occurs without incorporation of deuterium.[9]

A mechanism, known for other nucleophiles, [10] involving an addition-elimination of the phosphine could be proposed in agreement with recently described similar isomerization catalyzed by PPh_3 during catalytic hydration of diethylmaleate with palladium complexes in aqueous medium.[11]



The stereospecific hydrolysis of vinylphosphonium salts and the catalytic cis-trans isomerization of disubstituted olefins demonstrate that water-soluble phosphines such as TPPMS or TPPTS are useful versatile reagents for the reduction of acetylenic derivatives in water leading, by simple control of the stoechiometry, to a mixture of cis and trans olefins or specifically to the trans olefins (Table). Moreover, in D_2O, dideuterated olefins are obtained. The stereospecific hydrolysis and the fact that water does not interfer in the isomerization process account for the specific monodeuteration already described by sequential use of H_2O and D_2O.[2]

Table : Reaction of water-soluble phosphines with alkynes **3**.

Substrate	Molar ratio 3/1 or 2	Solvent	Reaction time	Product	trans/cis (c)
3a	1.2 (a)	H_2O	5 mn.	**5a**	70/30
	0.9 (a)	H_2O	3 h.	**5a**	≥ 99/1
3b	1.2 (a)	H_2O (D_2O)	5 mn.	**5b** (**5b** 2D)	60/40
	0.9 (a)	H_2O (D_2O)	1 h.	**5b** (**5b** 2D)	≥ 99/1
3c	1.2 (b)	H_2O	1 h.	**5c**	70/30
	0.9 (b)	H_2O (D_2O)	5 h.	**5c** (**5c** 2D)	≥ 99/1
3d	1.1 (a)	H_2O (D_2O)	5 mn.	**5d** (**5d** 2D)	30/70 (d)
	0.9 (a)	H_2O (D_2O)	1 h.	**5d** (**5d** 2D)	≥ 99/1 (d)
3e	1.1 (a)	H_2O (D_2O)	24 h.	**5e** (**5e** 2D)	30/70 (e)
	0.9 (a)	H_2O (D_2O)	6 days	**5e** (**5e** 2D)	≥ 99/1

(a) **1** ; (b) **2** was used since the zwitterionic trisulfonated vinylphosphonium salt hydrolyzes in neutral medium, when **1** is used **5c** is obtained upon addition of base ; (c) the products were isolated by extraction with ether or dichloromethane and the cis/trans ratio determined by GC/ms and ^1H NMR or ^2H NMR for deuterated products ; (d) **5d** trans precipitates in the reaction medium and has been isolated by filtration ; (e) cis and trans isomers have been separated by column chromatography.

The cis-trans isomerization catalyzed by water-soluble phosphines could be of interest to obtain specifically trans disubstituted olefins from cis or cis-trans mixtures under very mild conditions (room temperature, neutral pH). Moreover, the recovery of the organic product is easy and the small catalytic amount of phosphine required, separated in the aqueous phase, can efficiently be reused.

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3 - Vinylphosphonium salts **4d-e** are highly unstable and are instantaneously hydrolyzed whatever the experimental conditions.

4 - The reactions are quantitative ; the vinylphosphonium salts (Z and E isomers) were identified and quantified by ^{31}P NMR spectroscopy of the aqueous solution ; δ ppm : **4a** Z : 25.2 ; **4a** E : 25.8 ; **4b** Z : 21.3 ; **4b** E : 24.1.

5 - Identified and quantified by GC analysis and NMR spectroscopy after extraction with ether. The ^{31}P NMR spectra of the aqueous phases show that phosphine oxide is the unique phosphorus compound (34 ppm).

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7 - The ^{31}P NMR spectrum of the aqueous phase demonstrates that the phosphine remains unchanged (**1** : - 5.5 ppm).

8 - Pure cis **5e** or mixtures of cis and trans **5a** (30/70) , treated at room temperature with aqueous neutral solution of **1** (0.1 eq.), also give rise quantitatively to trans olefins. The reaction rate depends on the electronwithdrawing power and on the steric hindrance of the substituents (**5d** > **5a** >> **5e**). Isomerization does not occur in the absence of **1** or **2** excepted for cinnamaldehyde.

9 - Moreover, the protonated alkylphosphonium salt **6** $\geqslant\overset{\oplus}{P}-CH(CO_2Me)CH_2CO_2Me, Cl^{\ominus}$ is not an intermediate since its hydrolysis gives rise to a mixture of maleate, fumarate and succinate diesters (relative ratios 25/25/50). **6** has been prepared by reaction of **1** with **5d** (cis) in acidic medium (1.5 eq HCl).

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