

DOUBLE BOND MIGRATION OVER SOLID KOH
SUSPENDED IN APROTIC SOLVENTS

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Abstract - KOH suspended in DME is a good reagent to effect olefin double bond migration, especially deconjugation of α -enones.

It is well known that olefinic hydrocarbons possessing allylic hydrogen atoms undergo isomerization under the catalytic influence of strong bases such as, potassium amide, lithium-ethylene-diamine system, and organosodium compounds¹; the ease of double bond migration depends on the strength of the base. The solvent effects on the catalytic activity of potassium t-butoxide have been studied^{2,3}. More recently, a kinetic study was reported regarding the isomerization of allylbenzene under phase transfer conditions⁴.

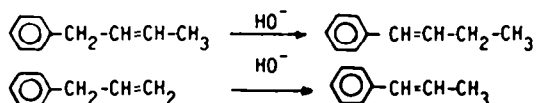
The olefinic double bond migration in α,β -unsaturated ketones leading to deconjugated ketones has received particular attention because of the importance of chemical and enzymatic enolization reactions. Thus, deconjugation of steroidal Δ^4 -3-ketones has often been accomplished by indirect means, e.g., via enol esters⁵⁻⁸. However, the direct conversion of α,β - to β,γ -unsaturated ketones was effected by acetic acid irreversible protonation of the conjugate anion derived from treatment of Δ^4 -3-keto-steroids with potassium t-butoxide in t-butanol, diglyme or DMSO^{9,10}.

It is well known that potassium hydroxide suspended in an aprotic solvent is a strong base^{11,12}. It can replace alkali hydrides, amides or t-butoxides in various reactions, e.g., in the production of carbanions^{13,14} and ketone or aldehyde enolates¹⁵. KOH is an especially cheap reagent and, in a suitable solvent, it is sometimes more effective than phase transfer conditions¹⁵.

We performed double bond migrations of phenylalkenes and α -enones using either powdered KOH suspended in various solvents (dehydrated by fusion, KOH_f : water content = 5 %) or undehydrated KOH_{nf} (water content = 15 %).

I - Isomerization of alkenes

We examined the action of potassium hydroxide in various solvents on the double bond migration in 1-phenyl-but-2-ene and 1-phenyl-prop-2-ene



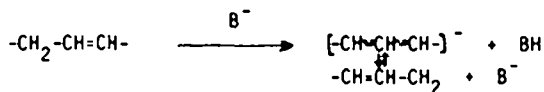
A suspension of 12 equivalents of KOH in 10 ml of solvent with 10^{-3} mole of alkene was heated at 40° or 60° C, with stirring. Analysis of the reaction products was performed by GPC on a GIRDEL apparatus (Column: 1,25 m, OV 225 (15 %); oven temperature: 110° C; N_2 pressure: 1 bar; internal standard: tetradecane).

No polymerization was observed.

As anticipated³, the migration of the terminal double bond is faster than that of the internal one.

A large excess of KOH is necessary to obtain the optimum reaction conditions. In reaction 1 (DME as solvent) 1.5 to 2 equivalents of t-BuOK were necessary to obtain better results (table II).

The mechanism suggested by several authors for the base-catalyzed isomerization of alkenes involves the formation of an allylic carbanion followed by reprotonation³.



In our case, the deprotonation step takes place at the surface of KOH. This can explain the necessity of a large excess of this reagent in order to shift the deprotonation equilibrium to the product side. Moreover, in aprotic solvents, the proton source is water formed during the reaction as well as water contained in the powdered KOH. Thus, it is understandable that undehydrated KOH ($\text{KOH}_{\text{H}_2\text{O}}$) is a somewhat better reagent than dehydrated KOH (KOH_f), even though solvation of HO^- by water decreases its basicity.

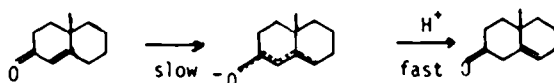
The reaction rate increases with increasing donor number of the solvent, viz., toluene (0.1) < dioxane (14.8) < DME (= 24), as in homogeneous media. The basicity of HO^- increases with increasing surface solvation of the associated cation K^+ .

II - Deconjugation of α,β unsaturated ketones

The chosen ketones were pulegone and the following polycyclic α -enones: $\Delta^{1,9}$ -octalone-2, $\Delta^{1,9}$ -10-methyloctalone-2, acetyltestosterone, progesterone, 4-androstene-3, 17-dione and cholestone.

A mixture of the ketone (10^{-3} equiv.) and powdered KOH ($12,5 \times 10^{-3}$ equiv.) was stirred in DME (10 ml for steroidal ketones, 5 ml for the other ones), at room temperature. After two hours or more (see the table) 10 % acetic acid was added, then an excess of aqueous sodium bicarbonate. The reaction product was extracted with ether and analyzed by NMR spectroscopy in CDCl_3 using anisole as an internal standard (60 MHz VARIAN spectrophotometer).

As in previous work concerning deconjugation by potassium t-butoxide in homogeneous media⁹, the amount of conjugated ketone recovered varies with the nature of the α,β -unsaturated ketone and, furthermore, the rate of deconjugation is governed by the slow rate of conjugate anion formation (table III).



In the case of $\Delta^{1,9}$ -octalone-2, the composition of the reaction mixture is similar to that obtained with tBuOK/tBuOH: 1 : 15 %, 2 : 55 %, 3 : 30 %. However, in t.BuOH, it has been shown that the proportion of 3 increases with reaction time, because of the isomerization of 2 to 3¹⁶. In our case, the 2/3 ratio does not vary in the course of the reaction, so the latter isomerization does not take place.

Acetyltestosterone gives the same results as testosterone: the acetyl function is hydrolysed due to the competitive nucleophilic attack of HO^- on the carbonyl group.

The deconjugation of keto-steroids is slower than that of pulegone or octalones. Even with t.BuOK/t.BuOH, the deconjugation of steroidal $\Delta^{4,5}$ 3-ketones was previously observed to be slow, and a large excess of base (10 equiv.) was necessary to obtain a good yield in 1.5 h⁹. In the case of steroidal polycyclic skeletons, the proton is less accessible than in mono or bi-cyclic enones. In the case of cholesterol where the reaction is especially slow, the alkyl chain can bend above the steroidal system and hinder the attack of HO^- .

As in the case of alkene isomerization, the dehydration of KOH by fusion does not enhance the rate of deconjugation. A similar possible explanation is that the presence of water can favour the reprotonation of the intermediate anion, thus displacing the deprotonation equilibrium in favour

of the products.

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Table I : Isomerization of $C_6H_5-CH_2-CH=CH_2$ at $40^\circ C$				
Solvent	Base	Reaction time	Yield %	
Toluene	KOH_f	20 h	25	
Dioxane	"	15 min.	15	
		30 "	40	
		60 "	70	
		90 "	86	
		120 "	87	
DME	"	5 "	53	
		30 "	100	
		KOH_{nf}	5 "	43
			30 "	100

Table II : Isomerization of $C_6H_5CH_2-CH=CH-CH_3$ at $60^\circ C$				
Toluene	KOH_f	20 h	0	
Dioxane	"	2 "	13	
		4 "	21	
		20 "	57	
DME	"	1 "	52	
		4 "	75	
		KOH_{nf}	1 "	56
			4 "	83
DME	10 equiv.	30 min.	= 95	
	5 "	30 "	= 95	
	2,5 "	30 "	90	
	tBuOK	2 "	40 "	92
		1,5 "	40 "	73
		1 "	30 "	20
		0,5 "	30 "	3
			3 h 30 min.	5

Table III

KETONE	REACTION TIME (h)	YIELD %**	PRODUCT
Pulegone	2*	80	
$\Delta^{1,9}$ -octalone-2 <u>1</u>	2*	66% <u>2</u> + 20% <u>3</u>	<u>2</u> <u>3</u>
$\Delta^{1,9}$ -10-methyl octalone-2 <u>4</u>	2*	73	<u>5</u>
Acetyl- testosterone <u>6</u>	2, 15*	50 70	<u>7</u>
Testosterone <u>8</u>	2, 15*	50 70	
Progesterone <u>9</u>	3, 15*	40 77	<u>10</u>
4-Androstene 3,17-dione <u>11</u>	3, 15*	62 75	<u>12</u>
Cholestenone <u>13</u>	15 r.t. 20, 40°	0 40	<u>14</u>

* No further change occurred after this time.

** In all cases, no products other than the unconjugated ketone were apparent.

NMR in DCl_3 , internal standard : anisol 3,70 s (3 H) ; 2-isopropenyl-5-methylcyclohexanone : CH_3 (5) 1,00 (s) ; CH_2 = 4,73. 1 : CH= 5,70 ; 2 : CH= 5,36 ; CH_2 2,93 (m.). 3 : CH_2 2,69 (m.) ; CH_3 (10) 1,20. 4 CH= 5,63. 5 CH= 5,3. 6 CH_3CO 2,03 : CH= 5,70. 7 CH = 5,30. 9 : CH= 5,70 ; 10 CH= 5,33 ; 11 CH= 5,73. 12 CH= 5,36. 13 CH= 5,66 ; 14 CH= 5,30.