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Substituent Effect on the Chemical Behaviour of some Carbonyl Compounds and Ketals with 1-Ethoxy-3-Trimethylsilylprop-1-yne

D. Zakarya[a*], A. Rayadh[a*], M. Samih[b] and T. Lakhlifi[a]

a) Département de Chimie, Faculté des Sciences, Meknès , Morocco
b) Département de Mathématiques et d'Informatique, Faculté des Sciences, Meknès, Morocco.

Abstract: In this work, principal component analysis (PCA) was carried out on the basis of property descriptors for a set of carbonyl compounds and ketals. A principal component projection of the points representing the compounds showed that the chemical behaviour of the compounds with 1-ethoxy-3-trimethylsilylprop-1-yne is related to their chemical composition. The obtained structure-chemical behaviour information was used to design a space transition state of the studied reactions.

In a series of papers, principal properties have been reported for Lewis acids [1], aldehydes [2] and ketones [2]. Authors have discussed how the principal properties (measured by the significant components of the principal component analysis -PCA-) can be used to explore the entire reaction space. Each PCA component is a linear combination of the basic molecular descriptors used. To be of general and practical interest, authors have studied larger collections of compounds. Analysis of the PCA projection obtained by [2], showed that compounds were distributed according to their size and shape. The obtained PCA model could be an interesting tool in the prediction of the chemical behaviour of some compounds in the particular reaction cited (fig.1). Nevertheless, some ketones and aldehydes from our set were not included. In addition, no study of ketals was made in the literature. This suggested a study of our compounds (table) separately.

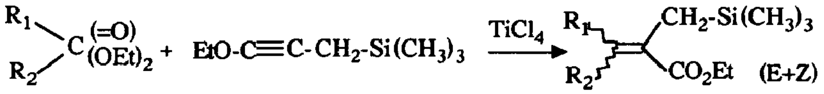

Figure 1 : Scheme of the studied reaction

Table : Chemical structures (R_1 and R_2) of the studied compounds.

Nr	R_1	R_2	Nr	R_1	R_2
1	H	CH_3 *(81)**(70)	**2**	H	$CH_3CH{=}CH$*(84)**(80)
3	H	$CH_3CH{=}CHCH{=}CH$**(88)	**4**	H	$(CH_3)_2CHCH_2$*(75)**(68)
5	H	$(CH_3)_2CH$**(67)	**6**	H	$CH_3(CH_2)_2$*(78)
7	CH_3	$CH_3OCH_2C{\equiv}C$*(39)	**8**	H	$Cl(CH_2)_4$*(70)
9	H	$nC_4H_9C{\equiv}CCH_2$*(50)	**10**	H	C_6H_5*(67)**(35)
11	H	$C_6H_5C{\equiv}C$*(48)	**12**	H	Furyl*(60)
13	H	Thienyl*(20)	**14**	H	OC_2H_5*(71)
15	H	$CH_2{=}CHCH_2$*(48)	**16**	CH_3	CH_3*(92)**(50)

Table : continued

17	CH_3	C_2H_5*(82)**(40)	18	CH_3	$ClCH_2$*(70)**(0)
19	CH_3	C_6H_5*(44)**(10)	20	CH_3	$pClC_6H_4$*(56)
21	CH_3	OC_2H_5*(0)	22	CH_3	CH_3COCH_2**(0)
23	C_2H_5	C_2H_5*(67)**(41)	24	$ClCH_2$	C_6H_5*(4)
25	OC_2H_5	OC_2H_5*(0)	26	Cl	CH_3**(50)
27	Cl	$CH_3CH_2CH_2$**(30)	28	Cl	$(CH_3)_2CH$**(51)
29	Cl	$ClCH_2$**(0)	30	Cl	C_6H_5**(42)

*( ) : ketal and its corresponding yield; ** ( ): carbonyl compound and its corresponding yield; R_2 was chosen as the bulkier group. All the studied reactions were carried out with $TiCl_4$ as catalyst in CH_2Cl_2 according to [3].

Carlson et al.[2] have described the molecules using various global molecular descriptors e.g. melting point, molar volume and molecular weight. This approach is interesting, nevertheless it does not allow the evaluation of the influence of R_1 and R_2 on the chemical behaviour of the molecules. For example, it is well known that the enantioselectivity of the reduction of a carbonyl group depends on the properties of both R_1 and R_2 groups. According to this fact, we have characterized each compound by a collection of property descriptors (Van der Waals volume [4-6], molecular refraction [7], molecular weight and the lenght of the radical[8]) corresponding to their radicals R_1 and R_2 linked to it. These [5,6] properties account for the steric and the electronic aspect of the molecule. The shape of each radical was described using the ratio Vi/Li where Vi was the Van der Waals volume of the radical and Li its lenght [8]. Finally each radical was described by means of five variables and each molecule by means of ten variables. Each descriptor variable was scaled to unit variance in order to avoid distorting the variance through the use of different units of measurment.

The final data matrix (30x10) was subjected to PCA (Statitcf package[9]).The components F_1 and F_2 accounted for 79,3% of the total variance. The projection of the cloud of points, representing the molecules, on F_1-F_2 plane was sufficient to account for the relations existing between them in the initial data set (figure 2) .

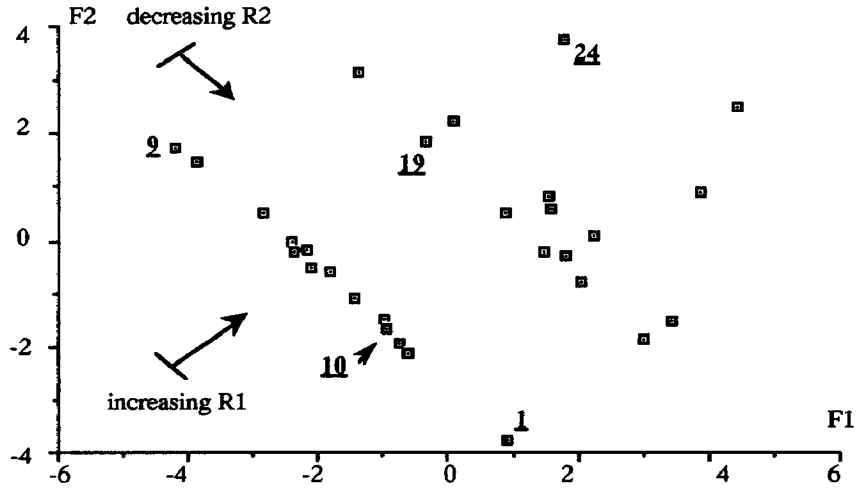

Figure 2 : F_1-F_2 projection of the points representing the compounds

Figure 2 shows that carbonyl compounds as well as ketals are distributed according to the size and the shape of R_1 and R_2. In addition, the projection gives the same information as that obtained by Carlson et al.[2]. We noted that carbonyl compounds as well as ketals leading to low yields were those possessing the bulkiest R_1 and R_2 groups. Then increasing R_1 and/or R_2 is unfavourable to the chemical affinity of the compounds with 1-ethoxy-3-trimethylsilylprop-1-yne. In opposite, the compounds (e.g. 1 and 16) leading to the higher yields correspond to small R_1 and R_2 groups. Analysis of data set reveals that R_1 is generally more unfavourable than R_2. These observations may be seen if one considers a linear relation between the experimental yield taken as a chemical affinity indicator, and descriptors coding R_1 and R_2.

$$\text{Yieldexp.} = -1.915\ V_1 - 0.856\ V_2 + 109.163$$

n = 20 (without the outliers 11 and 19), r = 0.723, s = 17.8; the coefficients were statistically significant at 95%. Despite its quality, this equation is in good agreement with PCA projection. The negative signs of the coefficients associated with both R_1 and R_2 showed that the size of these radicals (then their steric effects) is unfavourable to the chemical behaviour of the carbonyl compound in the considered reaction. A similar relation was obtained for ketals :

$$\text{Yieldexp} = -4.578\ V_1 - 0.494\ V_2 + 102.623$$

n = 15 (without the outliers 12 and 16), r = 0.778, s = 18.52; the coefficients were statistically significant at 95%. All these observations led to the conclusion that the chemical behaviour of the studied ketals and carbonyl compounds towards 1-ethoxy-3-trimethylsilylprop-1-yne can be explained by the steric effect of R_1 and R_2 only. Considering parameters coefficients, we can conclude that reaction yield decreases by increasing R_2 or R_1 size, with a more important effect of R_1. On the basis of these observations and the fact that R_2 was chosen as the bulkier group, it was possible to elaborate a spatial transition state, of the studied reactions, which is complementary to that supposed by Miginiac et al.[3] (figures 3a and b). This transition state allows to predict that isomer Z must be obtained in the majority, and suggested that R_1 and R_2 were not involved in interactions with a given atom in the 1-ethoxy-3-trimethylsilylprop-1-yne. Investigation of literature[3] reveals that Z isomer is obtained alone when R_1 is a hydrogen atom, except for R_2 = furyl or thienyl. While a mixture of Z and E (with Z in the majority) is obtained when R_1 is not a hydrogen atom. In this case, both R_1 and R_2 are probably out of the plane in the transition state. A molecular mechanics study may be useful for complementary information about this hypothesis.

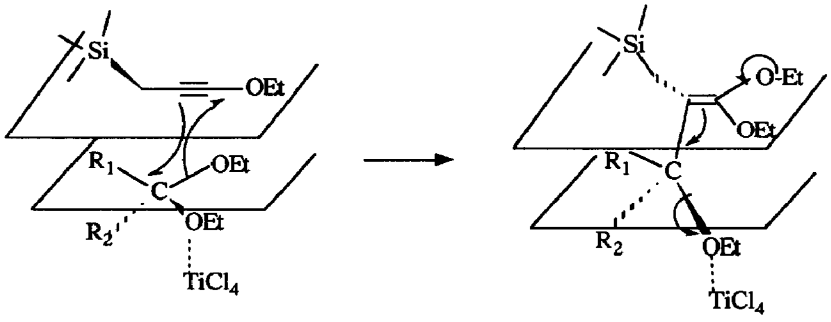

Figure 3a : Transition state for ketals

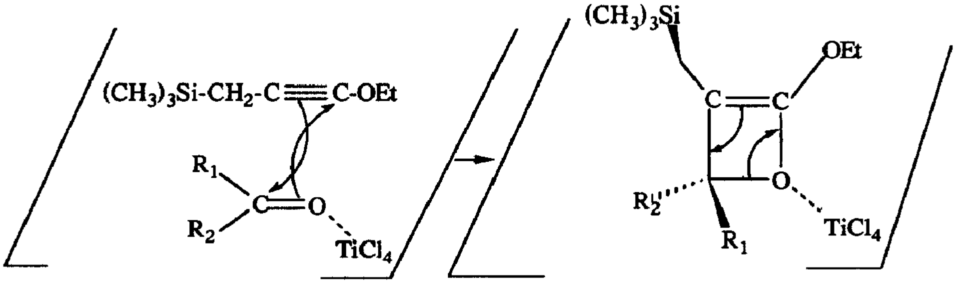

Figure 3b : Transition state for carbonyl compounds [10]

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8. Example of calculation of Li for some radicals (O=C-**Ri**), Li = 4 for Ri = propyl and Li = 3 for Ri = isopropyl. Li is considered as the smallest number of bonds between the carbon atom C of the carbonyl group and the farther atom,from C, of the radical.
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