

Substituent Effect on the Chemical Behaviour of some α -Halogenated Ketones and Aldehydes with 1-Ethoxy-3-trimethylsilylprop-1-yne

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Abstract: Principal Component Analysis (PCA) was carried out on the basis of property descriptors for a set of α -halogenated ketones and aldehydes. The obtained PCA model showed that the chemical behaviour of the compounds with 1-ethoxy-3-trimethylsilylprop-1-yne is related to the steric effect of the structural environment of the C=O group. Moreover the PCA model, the steric effect was underlined quantitatively with regression analysis models.

Principal properties have been recently investigated for several sets of Lewis acids¹ and carbonyl compounds². For such investigations, authors used the significant components of the principal component analysis (PCA) which are linear combinations of the basic molecular descriptors considered. Analysis of the PCA projection obtained² showed that the compounds were distributed according to their global 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 below (figure 1). However, the compounds used were not considered in earlier studies and our interest is focused on the effect of each substituent of the molecule on its chemical behaviour. Thus, in this work, we tried to study the substituent effects on the chemical behaviour of some α -halogenated carbonyl compounds with 1-ethoxy-3-trimethylsilylprop-1-yne using the PCA model as a qualitative approach and regression models as a quantitative one.

Data and statistical analysis

Seventeen compounds were tested as reactants with 1-ethoxy-3-trimethylsilylprop-1-yne³ (figure 1). All the reactions were carried out with TiCl_4 as catalyst in CH_2Cl_2 ⁴. As the 17 reactions were carried out in the same conditions, the experimental yield (Y%obs.) was considered as an approximative relative reactivity index. As the initial sample was not sufficient to make use of statistical methods with good reliability, we have extended the sample, to number 36 compounds.

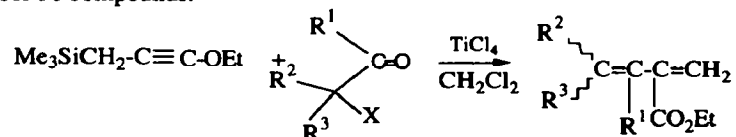


Figure 1 : Scheme of the studied reaction (X = Cl, Br)

Table 1: Chemical structures (R^1 , R^2 , R^3 and X) of the compounds studied. In order to obtain the same description for all the molecules, R^2 was chosen as the bulky group.

Nr	R^1	R^2	R^3	X	Y%obs.	Nr	R^1	R^2	R^3	X	Y%obs.
1	H	CH ₃	CH ₃	Cl	63	2	H	CH ₃	CH ₃	Br	60
3	H	C ₂ H ₅	H	Cl	0	4	H	C ₂ H ₅	H	Br	-
5	H	CH ₃	H	Cl	-	6	H	(CH ₃) ₂ CH	H	Cl	0
7	H	C ₆ H ₅	H	Cl	0	8	CH ₃	H	H	Cl	50
9	ClCH ₂	H	H	Cl	54	10	C ₆ H ₅	H	H	Cl	22
11	CH ₃	CH ₃	H	Cl	70	12	CH ₃	Cl	H	Cl	57
13	CH ₂ CH ₂ *	CH ₂ CH ₂ *	H	Cl	56	14	CH ₂ CH ₂ *	CH ₂ CH ₂ *	H	Br	55
15	CH ₂ CH ₂ *	CH ₂ *	H	Cl	-	16	CH ₃	C ₂ H ₅	CH ₃	Cl	0
17	CH ₃	CH ₃	CH ₃	Cl	-	18	CH ₃	Cl	Cl	Cl	44
19	(CH ₃) ₂ CH	CH ₃	CH ₃	Br	0	20	CH ₃ CHBr	CH ₃	H	Br	0
21	CH ₃	H	H	Br	-	22	CH ₃	CH ₃ CO	H	Cl	0
23	C ₂ H ₅	H	H	Br	-	24	H	H	H	Cl	-
25	C ₆ H ₅	H	H	Br	-	26	C ₆ H ₅	CH ₃	CH ₃	Br	-
27	H	Cl	Cl	Cl	-	28	p.Br-C ₆ H ₄	H	H	Br	-
29	p.Cl-C ₆ H ₄	H	H	Br	-	30	H	Br	Br	Br	-
31	C ₆ H ₅	Cl	H	Cl	-	32	p.CH ₃ C ₆ H ₄	H	H	Br	-
33	p.CH ₃ OC ₆ H ₄	H	H	Br	-	34	p.F-C ₆ H ₄	H	H	Cl	-
35	2,4-diClC ₆ H ₃	H	H	Cl	-	36	2,4-CH ₃ OC ₆ H ₃	H	H	Br	-

* Compounds having R^1 and R^2 as substructures of a group (cyclohexyl or cyclopentyl).

Compounds are finally coded by means of a vector the components of which represent variable descriptors of R^1 , R^2 , R^3 and X. The vector descriptor takes into account the size, shape, topology and electronic aspect of the radicals. The molecular properties used were van der Waals volume ⁵, molecular weight, molar refraction ⁶ and the radical length ⁷.

The shape of each radical was described using the ratio V_i/L_i where V_i is the van der Waals volume of the radical and L_i its length (smallest number of bonds between the carbon atom C of the carbonyl group and the farther atom, from C, of the radical). As example, L_i takes the value 3 and 4 for isopropyl and propyl groups respectively.

Finally each radical was described by means of five variables. The halogen atom was described with its molar refraction only. A binary variable (presence or absence of a given halogen atom) could be sufficient, nevertheless, we used the molar refraction, which takes into account both the size and the electronic aspect of the halogen, as descriptor in order to have a quantitative description. The data matrix obtained (36x16) was first subjected to PCA ⁷. Each variable was scaled to unit variance in order to avoid distorting the variance through the use of different units of measurement.

Results and Discussion

The components F_1 and F_2 accounted for 73.2% of the total variance. Then the projection of the cloud of points, representing the molecules, on the F_1 - F_2 plane was sufficient to account for the relations existing between them in the initial data set (figure 2). The projection above shows that the studied compounds are distributed into two different regions; one includes the compounds whose R^3 group is a hydrogen atom and the other includes the compounds corresponding to $R^3 \neq H$. Component F_2 seems to be a discriminant factor between these two categories of compounds, then taking into account the R^3 effect. F_1 is a discriminant factor between compounds with R^1 variable (R^2 constant and $X = Br$) and those with R^2 variable (R^1 constant and $X = Cl$). Moreover to their classification into four classes, points representing compounds are distributed essentially according to the size and the shape of the varying radical.

The variables coding R^1 and R^3 are well correlated (positive correlation with F_1 and F_2 respectively). R^2 is also well correlated with F_1 , but the correlations are negative. The variable coding the halogen is slightly correlated with both F_1 and F_2 . This reveals that the nature of the halogen may be not very important on the chemical behaviour of the compounds.

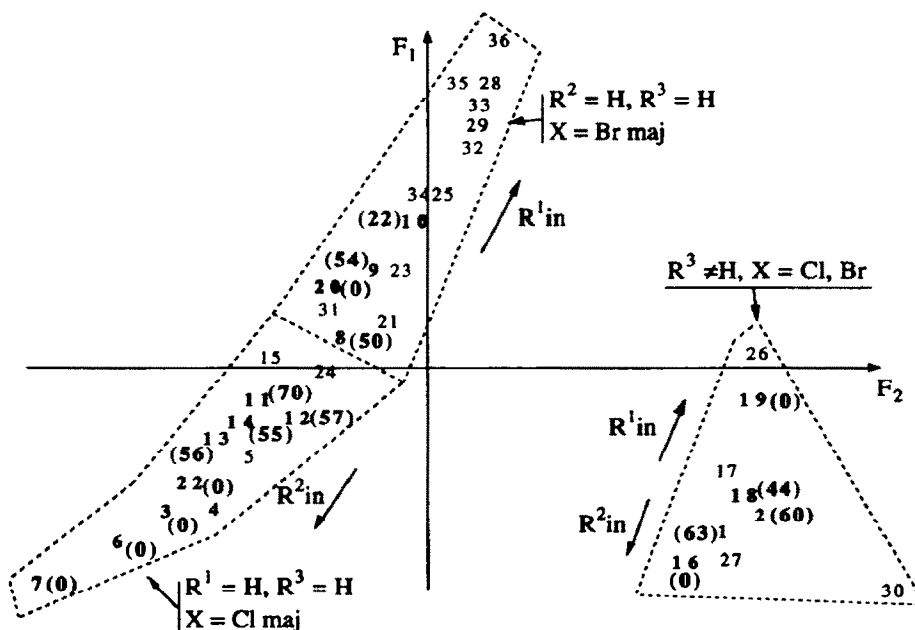


Figure 2 : F_1 - F_2 projection of the points representing the compounds. in : increasing; maj : in majority. Compounds drawn in bold are those tested with 1-ethoxy-3-trimethylsilylprop-1-yne. Their reaction yields are given into brackets.

When the distribution of the tested compounds (in bold) on the F_1 - F_2 projection was analysed, it was mainly noted that the experimental yield decreases when the environment (R^1 , R^2 , R^3 , X) of the $C=O$ group increases. The effect of the halogen is not very important as mentioned above. The PCA model underlined of the steric effect of radicals on the chemical behaviour of the carbonyl compounds. In addition to the qualitative analysis, it was interesting too, to evaluate quantitatively the substituent effect of each radical. Thus, we

attempted to establish structure-chemical behaviour relations between the experimental yield and the molecular descriptors used. As influence of the halogen was not very important, we elaborated a relation that included only the Van der Waals volume of R^1 , R^2 and R^3 .

$$Y\% = -1.349 \text{ VWR}^1 - 2.192 \text{ VWR}^2 - 0.864 \text{ VWR}^3 \quad (n = 17, r = 0.73, s = 21.87) \quad (1)$$

Despite the lower correlation coefficient, the obtained relation reveals the unfavorable steric effects of the three radicals. Their associated coefficients were all negative, and that associated with R^3 was not statistically significant. This is due to the fact that only few compounds with different R^3 groups were tested with 1-ethoxy-3-trimethylsilylprop-1-yne. The quality of equation (1) may be enhanced by suppressing some outliers or considering the interactions between variables.

Contributions of variables coding R^1 , R^2 and R^3 , according to the Gore method⁸ were 37%, 54% and 9% respectively. Considering these contributions values and the coefficients associated with the variables in equation (1), R^2 is the most unfavourable, followed by R^1 . R^3 seems to be of minor importance.

The results obtained were very useful in improving the design of the transition state (figures 3) initially proposed by Miginiac et al.³ for the studied reactions. This may be a tool to understand the stereochemistry of the obtained products^{9,10}. A molecular mechanics study is necessary for complementary information about this hypothesis.

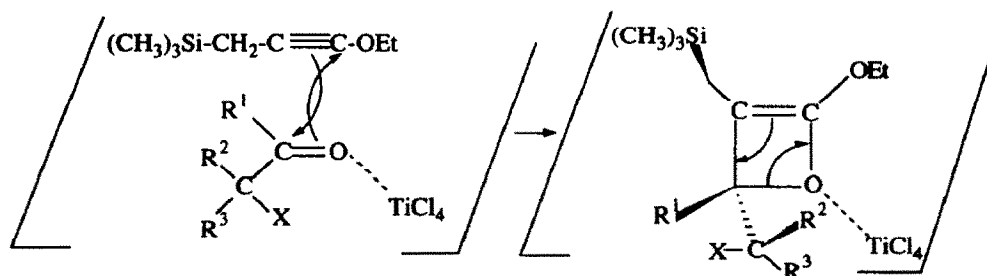


Figure 3: ³D design of the transition state on the basis of the substituent effect study.

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