HETEROCYCLES, Vol. 23, No. 10, 1985

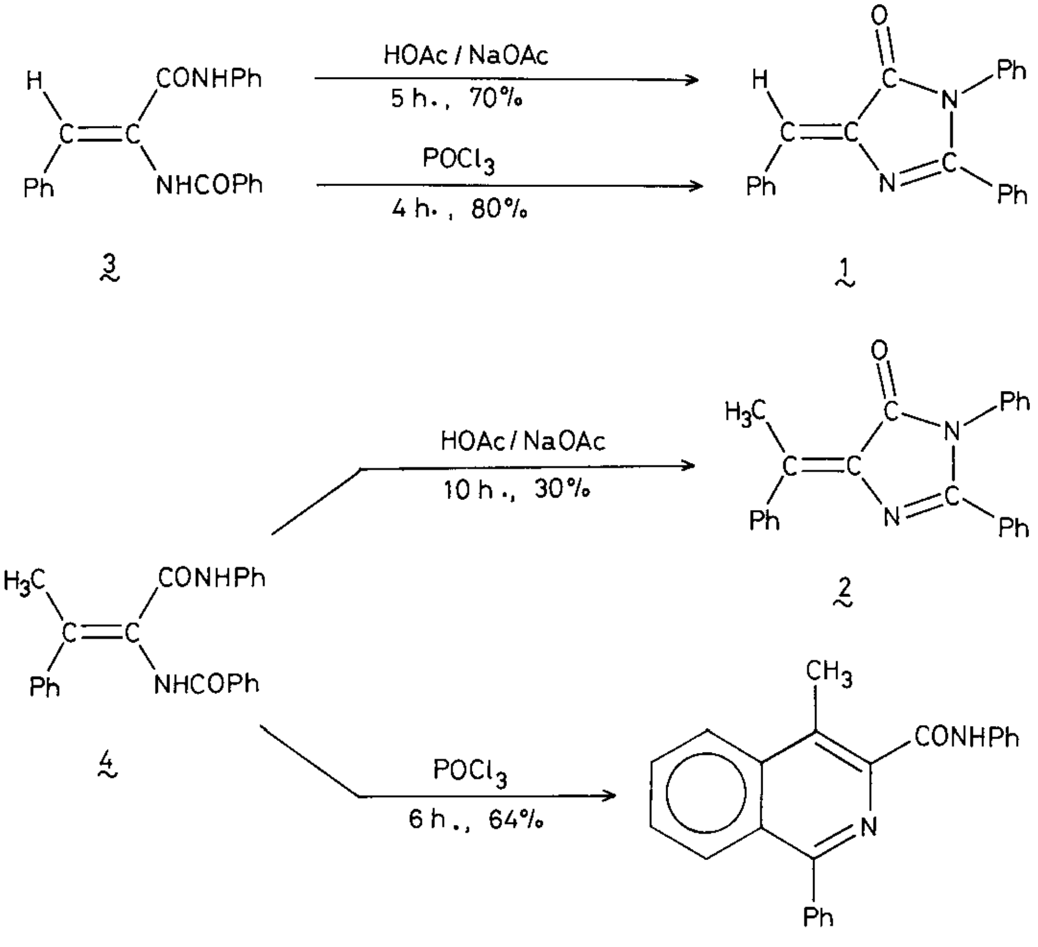
ON THE SYNTHESIS OF UNSATURATED 4(5H)-IMIDAZOLONES.2. SEMI-EMPIRICAL SCF-MO(MNDO) STUDY ON GEOMETRIC FACTORS INFLUENCING THE REACTION COURSE

Carlos Cativiela[1], José I. García[1], Carlos Jaime[2], José A. Mayoral[1] and Enrique Meléndez[1]
[1]Departamento de Química Orgánica, Universidad de Zaragoza, Zaragoza, Spain
[2]Departamento de Química Orgánica, Universidad Autónoma de Barcelona, Bellaterra (Barcelona), Spain

Abstract ——— Semi-empirical calculations by MNDO are achieved in order to explain the different reactivities of parent structures of anilides of (Z)-2-benzamidocinnamic acid and (Z)-2-benzamido-3-phenyl-2-butenoic acid to give the corresponding 4(5H)-imidazolones in the same conditions.

We have recently reported[1] some observations with regard to the synthesis of (Z)-2,3-diphenyl-5-benzylidene-4(5H)-imidazolone (**1**) and (Z)-2,3-diphenyl-5-(α-phenylethylidene)-4(5H)-imidazolone (**2**) and the implied stereochemistry.
In that work, we described how the anilide of the (Z)-2-benzamidocinnamic acid (**3**) cyclizes in the presence of acetic acid and sodium acetate or phosphorus oxychloride to yield **1**. Similarly, the anilide of (Z)-2-benzamido-3-phenyl-2-butenoic acid (**4**) yields **2** in the presence of acetic acid and sodium acetate although the reaction time is considerably longer and the yield lower. However, very different results are observed when **4** is treated with phosphorus oxychloride, since the 1-phenyl-3-phenylaminocarbonyl-4-methylisoquinoline (**5**) is obtained (Scheme 1).
A slight structural difference between **3** and **4** (the presence of a methyl group apparently at a considerable distance from the reaction centre) seems to be of great importance in determining the final product and the yields obtained. Our aim has been to demonstrate the influence of this methyl group on the reaction pathway due to the modification introduced in the structure and geometry of the reaction intermediate.
Semi-empirical SCF molecular orbital calculations, obtained by means of the MNDO[2] approach, have been used throughout this work. Structures were fully minimized, with the exception of geometrical parameters related to phenyl rings. They were all

fixed equal to standard values[3], except for the dihedral angle denoting the phenyl ring-double bond planarity.



Scheme 1

The geometrical features obtained by MNDO calculations on the ground state of the amides of (Z)-benzamidocinnamic acid, 6, and of (Z)-3-phenyl-2-butenoic acid, 7, which can be considered models for 3 and 4, respectively, point to two facts(see Fig.1):

1) The amido group is twisted from the C=C plane in compound 7 but not in 6.
2) In both cases the phenyl rings have lost their coplanarity with the rest of the molecule.

Methyl group effect

While in conjugated systems like 6 and 7 one could expect complete planarity, the skeletal atoms of 7 determine three planes in its MNDO energy minimum; phenyl ring, C=C bond and amido group (Fig. 1). When 7 was obliged to be planar in relation to C=C and the amido group, its heat of formation (H_f) increased by 2.5 kcal/mole.

6

$\omega_{2-3-4-5} = -71.8°$

$\omega_{N-1-2-3} = 180.6°$

7

$\omega_{2-3-4-5} = -92.3°$

$\omega_{N-1-2-3} = -69.1°$

Figure 1

A detailed study of MNDO minimized structures for 6 and 7 enables us to conclude that the methyl group has an important steric effect on the carbonyl oxygen of the amido group (see bond angles in Fig. 1), even in a non-planar conformation. This buttressing effect can also be observed in the final reaction products 1 and 2. MNDO calculations on 9, 10, 11 and 12, taken as models for 1 (9 and 10) and 2 (11 and 12), clearly show the presence of this interaction (compare bond angles and non-bonded distances in Fig. 2).

The steric hindrance of the methyl group on the carbonyl oxygen belongs to the long-range non-bonded interactions of the 1,5-type, which are usually of the g(+)-g(-) type, as in pentane. However, in this specific case there are three eclipsed, or almost eclipsed, bonds (Fig. 3). This situation forces the carbonyl oxygen and one of the methyl hydrogens into close proximity. This interaction is similar, although smaller, than the one present in o-methylbiphenyl.

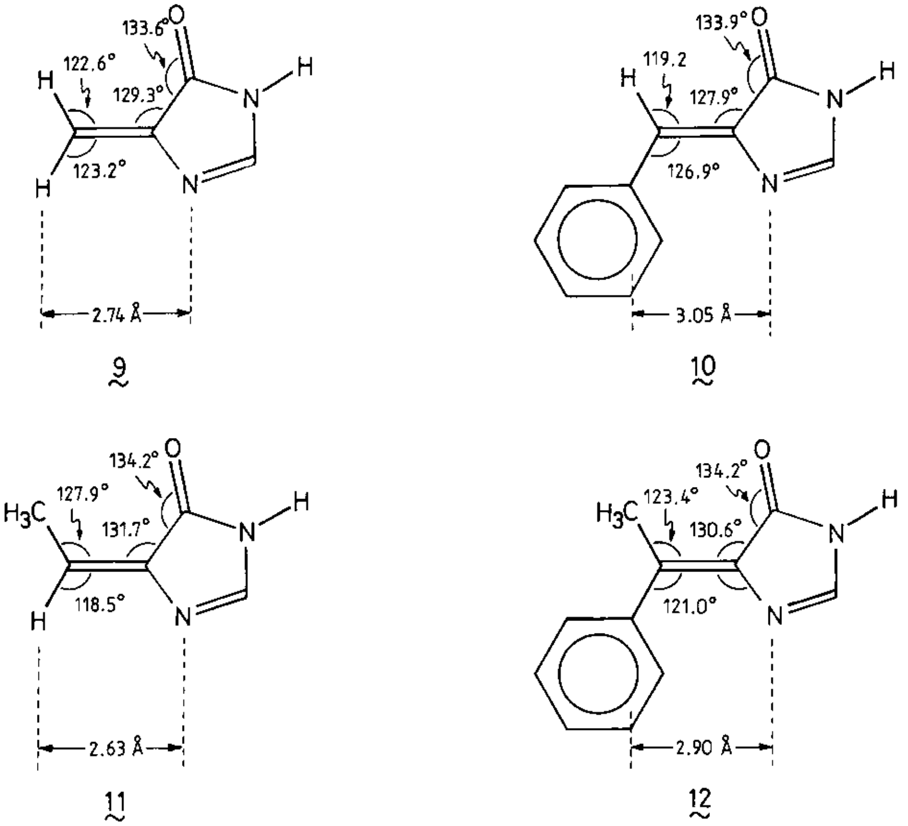


Figure 2

Figure 3

The presence of acidic media in the formation of imidazolones 1 and 2 is of fundamental importance. When 3, or 4, are placed in the presence of acetic anhydride-sodium acetate, 1 or 2, cannot be obtained. Furthermore, it is well known that amides are protonated on the carbonyl oxygen rather than on the nitrogen[4]. It therefore seems reasonable to regard charged (protonated) species as possible reaction intermediates.

The absence of coplanarity of the amido group and the C=C bond in the possible transition state is really important to explain why the reaction of 4 to form 2 does not take place easily. Obviously, imidazolone formation requires a cyclization step, which in turn needs almost perfect coplanarity of the five atoms intervening during cyclization (Fig. 4, intervening atoms are represented by the solid line).

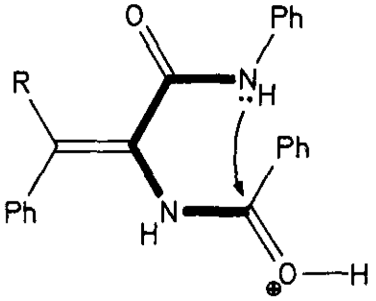
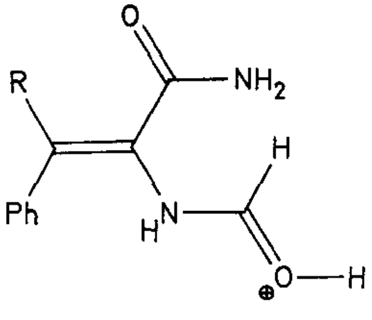


Figure 4

MNDO calculations on compounds 13 and 14, models of the hypothetical intermediates were carried out. Starting from a completely planar structure, with regard to skeletal atoms, minimization leads to non-planar geometries for both compounds. (Fig. 5).



13, R = H

14, R = CH_3

Figure 5

Dihedral angles N-C1-C2-C3 were of 134.1º and of 98.0º in **13** and **14**, respectively. Once again, the methyl group effect can be observed in the molecules studied. Considering **13** and **14**, good models for the real transition state for the cyclization reaction, the existence of such an effect and the consequent loss of planarity may account for the different behaviour of **3** and **4**. In compound **4** the presence of the methyl effect in the transition state will produce an unsatisfactory arrangement or will make it difficult to attain the adequate planar conformation, increasing the transition state energy and reducing the reaction rate and even the yield.

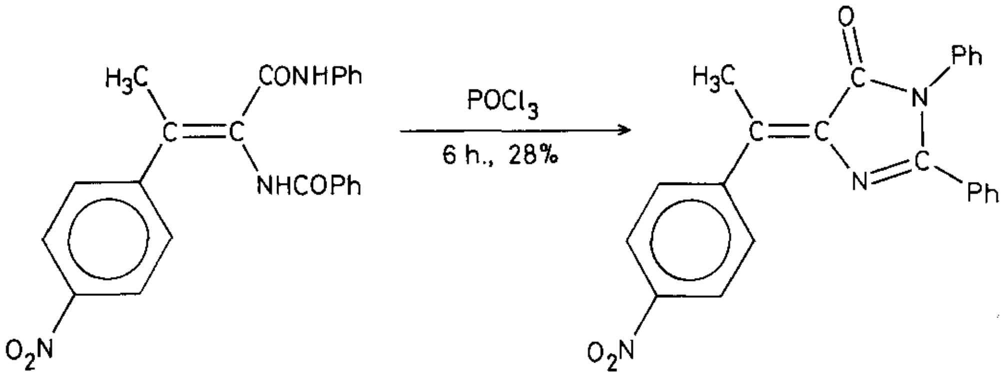
Phenyl ring-C=C coplanarity

Phenyl rings are out of the C=C bond plane in **6** and **7**. All MNDO calculations on related molecules, such as **10**, **12**, **13** and **14** show the same phenomenum.

The lack of planarity may be due to the MNDO tendency to twist groups with π-delocalization with phenyl rings[5,6], a tendency probably due to the overestimation of short non-bonded contacts in this semi-empirical method[2]. This situation in no way affects our present discussion. However, as it is of intrinsic interest work on it is in progress.

The former discussion about the influence of the methyl group on the cyclization of **3** to **1** and **4** to **2** would also be valid if a Lewis acid ($POCl_3$) were used instead a protic one. However, the situation is complicated by the possibility of a Bischler-Napieralski cyclization to the corresponding isoquinoline. Thus, while **3** cyclized largely to **1** (only traces of the corresponding isoquinoline could be detected by TLC), **4** cyclized to **5** in the same conditions.

It seems that the presence of the methyl group, which makes the cyclization to 4(5H)-imidazolone difficult, improves the appearance of isoquinoline derivative. However, when the anilide of (Z)-2-benzamido-3-(4-nitrophenyl)-2-butenoic acid (**15**), whose deactivated ring must prevent the Bischler-Napieralski reaction[7], was treated with phosphorus oxychloride, cyclization to (Z)-2,3-diphenyl-5-[α-(4-nitrophenyl)ethylidene]-4(5H)-imidazolone (**16**) occurred, as expected, without the appearance of the corresponding isoquinoline derivative and with a yield(28%) comparable to the cyclization of **4** to **2** with acetic acid (Scheme 2).



15 16

Scheme 2

EXPERIMENTAL

Melting points were determined on a Mettler FP 61 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer Model 283. NMR spectra were recorded on a Perkin-Elmer R-12 B Spectrophotometer with tetramethylsilane as the internal standard. Microanalyses were measured on a Perkin-Elmer 240-B analyzer and were in satisfactory agreement with the calculated values.

Preparation of 15:

(Z)-2-phenyl-4-[α(4-nitrophenyl)ethylidene]-5(4H)-oxazolone(6 mmol), prepared as previously described[8], and freshly distilled aniline(18 mmol) were refluxed in dry benzene (80 ml) for 20 h. The solution was then cooled and the precipitate filtered, washed with dry benzene and dried. One recrystallization from ethanol/water gave an analytically pure sample. The yield was 71%.

15: mp 252-253ºC (dec); colorless needles, ir(nujol)3300,3260,1660 cm^{-1}; ^1H-NMR (DMSO,d_6) δ 2.26(3H,s), 6.9-8.4(14H,m), 9.8(1H,s), 10.2(1H,s).

Preparation of 16:

Compound 15 (3 mmol) was refluxed in $POCl_3$ (4 ml) for 6 h. The solution was then cooled, poured on to crushed ice and the precipitate extracted with CH_2Cl_2. The extract was washed with aq.$NaHCO_3$ and dried over $MgSO_4$. The solvent was distilled off and the residue was recrystallized from ethanol/water. The yield was 28%.

16: mp 190-191ºC; yellow needles ; ir(nujol)1700 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.65(3H,s) 6.9-8.4(14H,m).

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Received, 3rd July, 1985