



Racionalization of the reaction routes involved in intramolecular cyclizations of δ -hydroxynitriles induced by triflic anhydride

Valeria Justribó, Silvina C. Pellegrinet and María I. Colombo

Instituto de Química Orgánica y de Síntesis (CONICET-UNR), Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, 2000 Rosario, Argentina. E-mail: mcolombo@fbioyf.unr.edu.ar

Introduction

Ritter's reaction, in the most general form, involves the formation of *N*-substituted amides by the addition of nitriles to alkenes or alcohols in the presence of concentrated acid (Ritter and Minieri, 1948; Krimer and Cota, 1969; Bishop, 1991). However, the scope of this reaction shows severe limitations due to the requirement of a strongly acidic medium. In order to overcome this problem several approaches have been developed which employ relatively mild conditions. One of them is proposed by Garcia Martinez *et al.* (1989) in which triflic anhydride in dichloromethane is used.

Ritter's reaction of nitriles is a good methodology for obtaining heterocyclic species. However, the intramolecular applications of Ritter's reaction using derivatives of alcohols are yet not much known (Krimen and Cota, 1969).

With the intention to study such reactions further, in the recent years we have developed the cyclization under study using δ -hydroxynitriles. The treatment of such substrates with triflic anhydride in dichloromethane led to surprising results. For example, bicyclic δ -hydroxynitriles selectively led to enones or lactones instead of lactames (Justribó and Colombo, 2003) (Fig. 1).

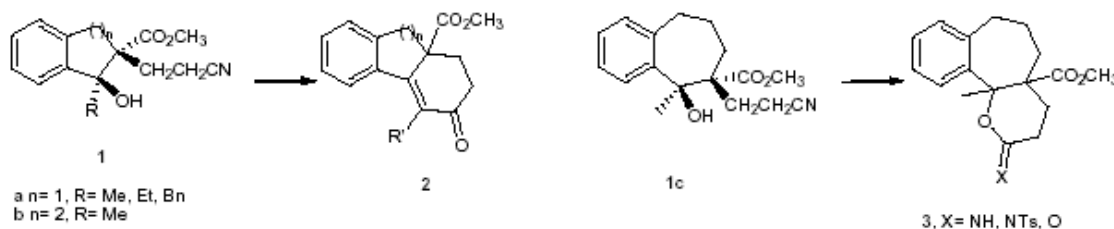


Figure 1

Our results suggest that when these reactions are catalyzed with triflic anhydride, the activated nitrile would be caught by the hydroxyl group or by the alkene, depending on the predisposition of the substrate to be dehydrated in the presence of the triflate ion to give lactones or enones.

Methodology

In order to investigate the reactivity pattern of these alcohols we have performed a theoretical B3LYP/6-31G* study. Therefore, we considered the alcohols **1a** (R = Me), **1b** and **1c** as targets. The conformers of minimum energy of some selected intermediates were

found by carrying out a conformational search using the MM+ method of Hyperchem 7.5. A large number of geometries were reoptimized with Gaussian at the RHF/3-21G and B3LYP/6-31G* levels of theory. In order to study the relative stabilities of the carbocations we have calculated their affinities for the hydroxyl ion. Therefore, we have optimized the geometries of the alcohols **1a**, **1b** and **1c** as well as those of their associated carbocations **1Ca**, **1Cb** and **1Cc** (Fig. 2).

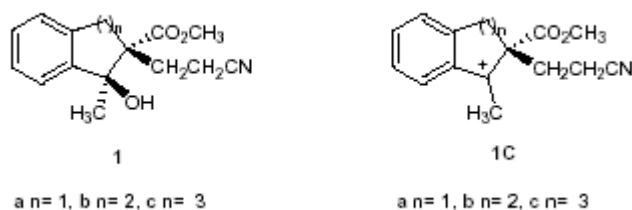


Figure 2

Results

The distances calculated between the hydrogen atom of the hydroxyl group and the oxygen atom of ester carbonyl group are shown in Fig. 3. These distances are significantly shorter than the sum of their respective van der Waals radii. This observation suggests that **1a**, **1b** and **1c** show hydrogen bridge-type stabilizing

interactions. Besides the oxygen-hydrogen distances decrease significantly with the increase of the ring size. This effect could be attributed to the higher ease of the six- and seven-membered rings to adopt conformations with optimal bond angles for such interactions.

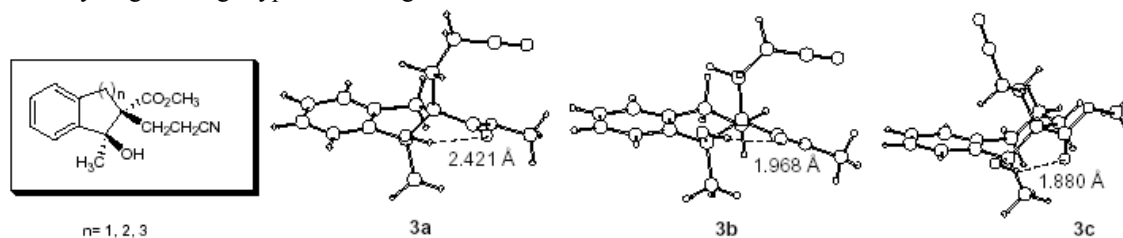
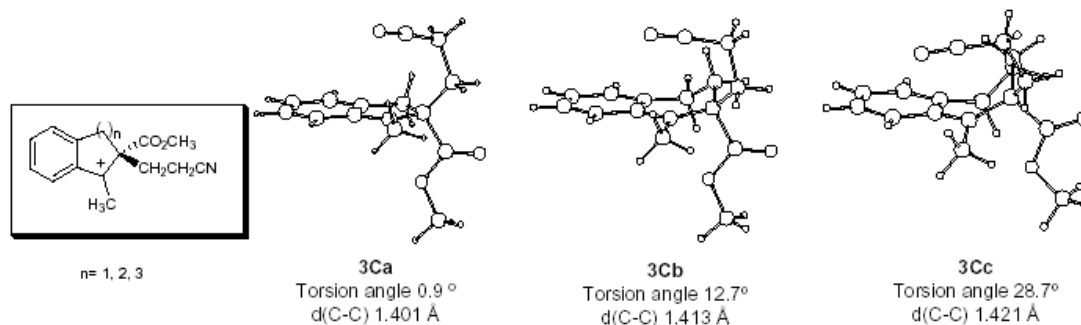


Figure 3. B3LYP/6-31G * geometries of the alcohols **1a**, **1b** and **1c**.

In the geometries of the conformers of minimum energy for carbocations (Fig. 4) can be observed that while the five-membered ring of the cation **1Ca** is almost planar, the six- and seven-membered rings of **1Cb** and **1Cc** exhibit an increasing off-plane deformation, which is oriented toward the upper surface of the molecule.

These conformations appear to be stabilised by an electronic interaction between the electron-deficient carbon atom and the cyano group.

Furthermore, the C-C-C-C torsion angles CCAM established between the methyl group and the aromatic carbon atom increase considerably with the ring size increase, thus suggesting that the carbocation **1Cc**, which has a seven-membered ring, should have a lower stabilisation by conjugation with the aromatic ring. The C-C calculated distances are in agreement with these observations taking into account that the greater the distance, the lower the effectiveness of the conjugation.



**Figure 4.** B3LYP/6-31G* geometries of the carbocations **1Ca**, **1Cb** and **1Cc**.

The extent of affinity of the carbocations **1Ca**, **1Cb** and **1Cc** for the hydroxyl ion is shown in Table 1. This turns out to be a good parameter to estimate the relative reactivity of such species. The calculated values suggest that as the ring

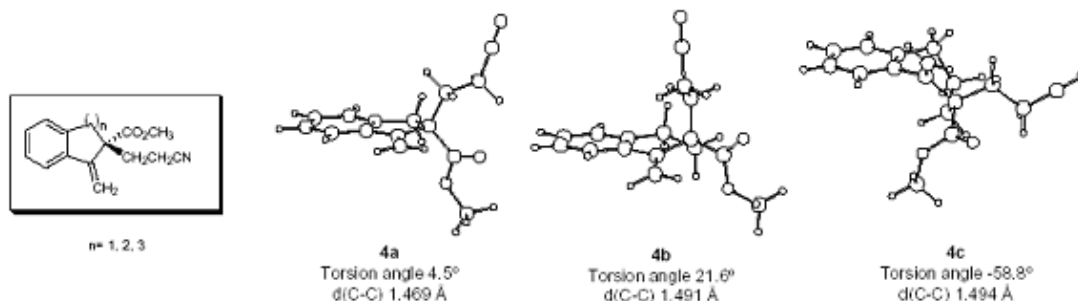
size increases the combination between the carbocation and the hydroxyl becomes more favourable, and therefore, it can be presumed that such cation is more reactive and less stable.

Table 1. ΔE_0 , ΔH and ΔG of the reaction of the carbocations **1Ca**, **1Cb** and **1Cc**.

Carbocation	ΔE_0 (Kcal/mol)	ΔH (Kcal/mol)	ΔG (Kcal/mol)
1Ca	-216.57	-218.32	-205.78 (6.54)
1Cb	-218.86	-220.48	-208.75 (3.57)
1Cc	-222.10	-223.70	-212.31 (0.00)

To estimate the relative acidity of the cations under study the energy changes involved in their deprotonation to generate the alkenes **4a**, **4b** and **4c** with the triflate ion were also calculated (Fig.

5). The deprotonation of **1Cc** seems to be the most favoured, which is in Agreement with the lower stability attributed to such cation (Table 2).

**Figure 5.** B3LYP/6-31G* geometries of the alkenes **4a**, **4b** and **4c**.**Table 2.** ΔE_0 , ΔH and ΔG of the deprotonation of the carbocations **1Ca**, **1Cb** and **1Cc** with the triflate ion to generate the alkenes **4a**, **4b** and **4c**, respectively.

Carbocation	ΔE_0 (Kcal/mol)	ΔH (Kcal/mol)	ΔG (Kcal/mol)
1C	-86.81	-86.81	-86.95 (4.83)
8aC	-86.12	-85.95	-86.63 (5.15)
8aaC	-91.12	-90.89	-91.78 (0.00)

Conclusions

These results suggest, at first instance, that the alcohol that has a seven-membered ring (**1c**) would be the least reactive of the compounds under study in dehydration reactions, and that the carbocation **1Cc** would be more unstable than the 5- and 6-membered analogues **1Ca** and **1Cb**. On this basis we could assume that the formation of **1Cc** is less favoured and, therefore,

that the hydroxyl group carries out the attack on the more quickly activated cyano group. This reaction pathway would lead to the formation of an imidate as main product.

On the contrary, the structures that have 5- and 6-membered rings would see more favoured the formation of the corresponding cations and alkenes because of having structural and electronic factors which provide them stability.



Taking into account these results we could expect that such compounds opt for the reaction route that involves the formation of alkenes,

which later by attack to the triggered cyano group would cause the formation of enones (Fig. 6).

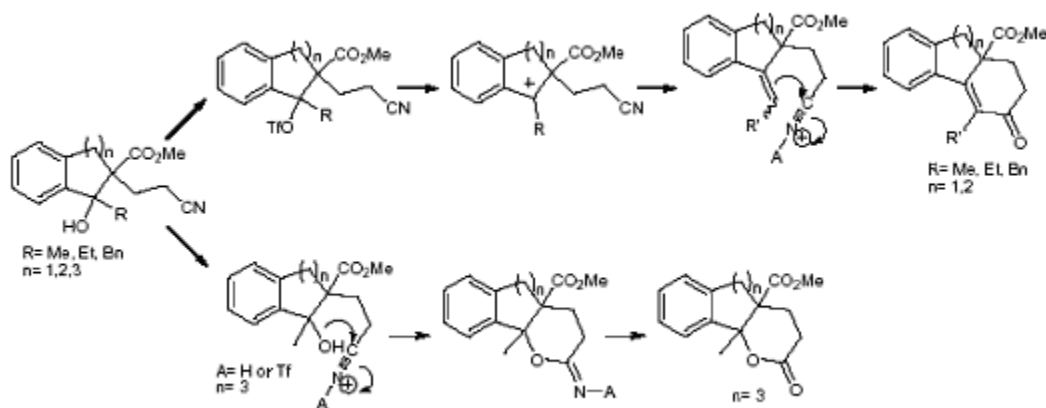


Figure 6

Note: This study was presented at the "XXVI Congreso Argentino de Química", San Luis, Argentina, 2006

References

- Bishop R. (1991) *Comprehensive Organic Synthesis*. Trost B. M., Eds., Pergamon Press, New York; Vol. 6, pp 261-300.
- García Martínez A., Martínez Alvarez R., Teso Vilar E., García Fraile A, Hanack M. and Subramanian L. R. (1989) An improved modification of Ritter reaction. *Tetrahedron Lett.* **30**, 581-582.

- Justribó V. and Colombo M. I. (2003) An unexpected result in an intramolecular Ritter reaction induced by triflic anhydride. *Tetrahedron Lett.* **44**, 8023-8024.
- Krimen L. I. and Cota D. J. (1969) *Organic Reactions*. Dauben, W. G. (ed.); John Wiley & Sons, New York; Vol. 17, pp 213-325.
- Ritter J. J. and Minieri P. P. (1948) A new reaction of nitriles. I. Amides from alkenes and mononitriles. *J. Am. Chem. Soc.* **70**, 4045-4048.