Molecular Medicinal Chemistry

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Synthesis and theoretical study of the reactivity of the heterocycle 2, 3-dihydroimidazo [1,2-*b*]isoquinolin-5(*H*)-one

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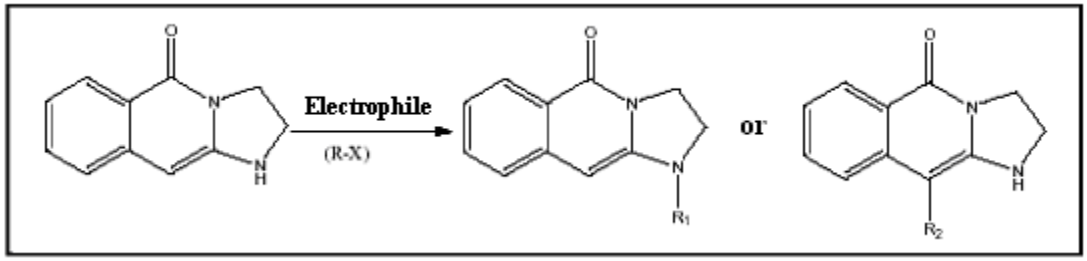
Introduction

Imidazoisoquinolinones are heterocycles of value for the development of new derivatives with potential antiparasitic activity. In our laboratory the synthesis of the base compound, 2,3-dihydroimidazo[1,2-*b*]isoquinolin-5(*H*)-one (**1**), was developed by microwave irradiation, from which by substitution reactions various derivatives were synthesized in order to obtain active compounds against *P. falciparum* and *T. cruzi* (Bollini *et al*., 2006). For the design of this compound and derivatives we based on their structural characteristics compared with different pharmacophores.

The aim of this work is to study the chemical reactivity of heterocycle **1**, mapping sites susceptible to substitution with different electrophiles (Scheme 1).



Scheme 1

Methodology and results

We observed experimentally that different electrophiles selectively yield substituted products in positions 1 and 10 of the "base" heterocycle (Table 1).

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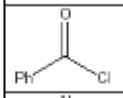
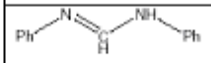
Table 1. C-10 substitution N-1 substitution

Electrophile	Product
Ph—CH_2Cl	10-Benzyl-2,3-dihydro-1*H*-imidazo[1,2-b]isoquinolin-5-one
Ph—N=C=S	10-[(*N*-Phenyl)thiocarbamoyl]-2,3-dihydro-1*H*- imidazo[1,2-b] isoquinolin-5-one
 + DMAP	10-[(Phenyl)carbonyl]-2,3-dihydro-1*H*-imidazo[1,2-b] isoquinolin-5-one

Electrophile	Product
	1-[(Phenyl)carbonyl]-2,3-dihydro-1*H*-imidazo[1,2-b] isoquinolin-5-one
	1-Phenyliminomethyl-2,3-dihydro-1*H*-imidazo[1,2-b] isoquinolin-5-one
Ph—N=C=O	1-[(*N*-Phenyl)carbonyl]-2,3-dihydro-1*H*-imidazo[1,2-b] isoquinolin-5-one

To justify experimental regioselectivity between heterocycle **1** and this set of electrophiles, we relied on the hard and soft theory of Pearson (HSAB), thus being able to analyse the selectivity of this compound.

The molecule reactivity is related to the system properties, such as hardness (η) and electronegativity (χ). Hardness is the resistance of the chemical potential (μ) to the change of electron number (N), as described in Eq. 1, where *E* is the energy of the system and ν is the external potential (Parr and Yang, 1984; Pearson, 1987).

$$\eta = 1/2(\delta\mu/\delta N) = 1/2(\delta^2 E/\delta N^2)\nu \quad \text{(Eq. 1)}$$

In Eq. 2 softness (*S*) is described, which is the inverse of hardness.

$$S = 1/2\ \eta \quad \text{(Eq. 2)}$$

Electronegativity is defined as the inverse of the chemical potential, and is the power of the system to attract electrons.

$$\chi = -(\delta E/\delta N)\nu = -\mu \quad \text{(Eq.3)}$$

Electronegativity and hardness of compound **1** were calculated, resulting in a globally soft molecule as results shown in Table 2.

On the other hand, total electronic energy, the energy of HOMO, LUMO and the energy difference between frontier orbital gap were calculated (Table 2). Large energy differences between HOMO and LUMO account for stable and low reactive systems, while the opposite case account for unstable and therefore reactive systems.

Energy difference calculated for heterocycle **1** is small, thus demonstrating to be a reactive system.

Ionization potential (IP) is defined as the amount of energy required to remove an electron of the molecule. Thus, a high value of ionization energy indicates that the system does not lose electrons easily.

Electronic affinity is defined as the related energy when an electron is taken by a neutral molecule. An atom or molecule with a high electron affinity tends to attract electrons more easily (Table 2).

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Table 2. Chemical parameters indicative of the reactivity of compound **1**.

Properties	Calculated data
Electronic affinity [$A=E_{(O)}-E_{(-1)}$] [$A=-E_{LUMO}$] (eV)	0.52
Ionization potential = [$I=E_{(O)}-E_{(-1)}$] [$I=-E_{HOMO}$] (eV)	4.92
Hardness [$\eta=(I-A)/2$]	2.175
Electronegativity [$\chi=(I+A)/2$]	2.745
Electrophilicity ($\omega=\mu^2/2\eta$)	1.73
Energy difference (gap)	4.4

While global system properties may explain the reactivity of a molecule, to understand selectivity Fukui *f* functions can be applied, three different, f^+, f^-, f^r, being determined, depending on whether the molecule behaves as nucleophile, electrophile, or radical (Eq. 4, 5 and 6).

$$f^+ = [\rho_{N+1} - \rho_N] \approx \sum C_{\alpha k}(LUMO)^2 + C_{\beta k}(LUMO)^2 \quad \text{(Eq. 4)}$$

$$f^- = [\rho_N - \rho_{N-1}] \approx \sum C_{\alpha k}(HOMO)^2 + C_{\beta k}(HOMO)^2 \quad \text{(Eq. 5)}$$

$$f^r = 1/2[f^+ + f^-] \approx 1/2\sum C_{\alpha k}(HOMO)^2 + C_{\beta k}(LUMO)^2 \quad \text{(Eq. 6)}$$

For the calculation of Fukui function, Frozen Core approach is used, which expresses Fukui function in terms of frontier orbital density (Ayers and Levy, 2000).

According to the rules of selectivity and reactivity of Li-Evans (Li and Evans, 1995), soft-soft interactions are determined by the maximum Fukui value, and hard-hard interactions are described through the minimal *f* value. In Fukui polyfunctional systems, is a good descriptor for soft-soft interactions, while often fails to describe hard-hard interactions, which are controlled by charges (Melin *et al*., 2004). Therefore, charges are proposed as best descriptors for these interactions (Li and Evans, 1995).

According to Fukui indices, C-10 and N-1 are nucleophilic sites on the molecule of heterocycle **1** (Table 3).

Table 3

	f⁻	q_M	NPA	EPS
C-10	0.1882	-0.306	-0.309	-0.664
N-1	0.1174	-0.714	-0.636	-0.625

From these data it can be concluded that C-10 is a soft nucleophilic center and N-1 is a hard center since it has a lower value of Fukui and a higher value of charge, being expected that interaction with soft electrophiles is favoured at position 10 of the heterocycle, and on N-1 preferentially react hard electrophiles.

Because heterocycle **1** reacts in a selective manner with different types of electrophiles, their hardness and softness were studied. The values of hardness, electronegativity, Fukui coefficients, and charges for phenylisocyanate, phenylisothiocyanate and diphenylformamidine were calculated.

Global results obtained for the calculation of hardness and electronegativity of these compounds suggest that all electrophiles are globally soft: Therefore, this result would not justify substitution with phenylisocyanate and diphenylformamidine at position 1 of the heterocycle, which accounts for a hard center (Table 4).

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Table 4

Electrophile	η(eV)	χ(eV)
Phenylisocyanate	2.965	3.60
Phenylisothiocyanate	2.5	3.78
Diphenylformamidine	2.365	3.045

Therefore, the reactivity of these compounds at local level was studied. The values of f^+ and q_M show that the reactive C of phenylisothiocyanate is softer than the rest of the studied electrophiles, which would explain their increased reactivity at the soft center level (C-10) of heterocycle **1**.

On the other hand, both the C of phenylisocyanate and of diphenylformamidine show a higher hardness, which is expressed with a lower Fukui coefficient value, and a higher charge, so that the attack at position 1 of the heterocycle (hard center) is favoured (Table 5)

Table 5

	Phenylisothiocyanate	Phenylisocyanate	Diphenylformamidine
$f^+(C)$	0.2375	0.1647	0.1621
$q_M(C)$	0.138	0.566	0.283

Experimentally we observed that the reactivity of heterocycle **1** with acylating agents is dependent on DMAP addition as catalyst. We have previously reported that catalyst leads to an acylated C-10 derivative through:
-A slow rearrangement mechanism, from *N*-acylated to acylated C-10 derivatives.
-A fast mechanism of DMAP acylation, and subsequent nucleophilic attack of heterocycle **1** to the acylating agent.

Based on these results, the reaction of heterocycle **1** with acylated DMAP was studied, leading to the substituted C-10 derivative, which was compared with the reaction of **1** with acylating agents without catalyst, thus providing the *N*-substitution product.

Table 6

	η(eV)	χ(eV)	ΔN
Acylated DMAP	2.3	8.33	0.62
Acetyl chloride	3.52	4.65	0.17

According to the results obtained for the reactivity study of acylated DMAP and acetyl chloride (Table 6), it can be observed that softer electrophile accounts for acylated DMAP for possessing a lower value of η, thus justifying the reactivity on the softest center of the molecule **1** (C-10).

The number of electrons transferred in a reaction (ΔN) can be determined as follows:

$$\Delta N = \chi_A - \chi_B / 2(\eta_A + \eta_B) \quad \text{(Eq. 7)}$$

Electronegativity difference is the driving force of the reaction, while the sum of hardness parameters inhibits electron transfer. The reaction of **1** with acylated DMAP is the most favoured as shown in Table 6.

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All computer calculations were carried out using density functional theory (DFT) of Gaussian03W program at the B3LYP/6-311++G(d,p) level.

Conclusions

- The theoretical reactivity study of the heterocycle 2,3-dihydroimidazo[1,2*b*]isoquinolin-5(*H*)-one allowed to explain experimental results, using pearson theory of hard and soft (HSAB).
- These theoretical studies will allow to predict the binding site of new electrophiles, and the rational design of new compounds in order to obtain derivatives with major trypanocidal activity.

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

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