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# HETEROCYCLIC COMPOUNDS: THEIR POTENTIAL APPLICATION AS ANTIMICROBIALS OF HEALTH IMPORTANCE AND IN THE CATALYTIC HYDROGEN TRANSFER REACTION

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**Abstract**: This article presents the results of the synthesis of compounds derived from 2-phenyl-1,8 naphthyridine and their application primarily as antimicrobial agents against strains of hospital importance of *Candida albicans*, *Escherichia coli* and *Staphylococcus aureus* strains. Then, the synthesized compounds were used together with $Ru_3(CO)_{12}$ as a catalyst for the hydrogen transfer reaction from acetophenone to 1-phenylethanol, identifying a new ruthenium complex and evidence on the factors that affect this reaction what is important in the pharmaceutical industry.
**Keywords:** Antimicrobial agent, 1,8-naphthyridine derivatives, ruthenium catalyst.

## INTRODUCTION

The synthesis of heterocycles, such as quinolones and naphthyridines, generates considerable interest among researchers due to their wide range of applications such as the synthesis of luminescent sensors for the detection of heavy metals in water, as well as light-emitting devices (OLEDs), preparation of complexes for homogeneous catalysis, among others.

Compounds derived from naphthyridines and quinolones are among the best-known antimicrobial agents, which are medicines that treat infections and reduce the length of stay of hospitalized patients. Among them are nalidixic acid and its derivatives, which possess antibacterial and antifungal activity. In general, these compounds present biological activity, since they interact with two enzymes, DNA gyrase and topoisomerase IV, respectively, interfering with DNA synthesis, causing bacterial cell death. (Agirbas, 2011).

For its part, naphthyridine is a system of two pyridine rings fused through adjacent carbon atoms, with six possible isomeric forms. While 1,8-naphthyridine derivatives could act as ligands for different metals, and they may bind the magnesium atom carbonyl groups in a hypothetical interaction with DNA gyrase instead the carbonyl groups as fluoroquinolones. (Chim, 2009) Outer membrane (OM) permeability can be modulated by incorporation cycles ring into the 2-position, leaving less hindered the plausible site with magnesium binding. Regard with the proposed, a model complex could be 2-phenyl-1,8-naphthyridine but structural features can be added to modelling new potential antimicrobial agents keeping in mind their mechanism against bacteria. (Rivero, 2014)

Regarding their coordination chemistry and organometallic compounds, the best studied heterocycles are 1,10-phenanthroline, 2,2'-bipyridine and 2,2'-biquinoline, which consist of two $sp^2$ nitrogen atoms which act as donors, forming stable 5-membered chelates with transition metals.

On the contrary, 1,8-naphthyridine has different coordination modes with metals, including 4-membered chelates or a monodentate mode, which can be an advantage during a transition metal-catalyzed reaction to allow the formation of sites vacancies or give stability to intermediates of the reaction mechanism.

In relation to the metal of interest in this study, ruthenium is well known for forming complexes in different oxidation states (0), (II) and (III) with nitrogenous binders, which are capable of catalyzing a wide variety of organic reactions. In particular, the ruthenium (0) complexes adopt the di-pyramidal-trigonal geometry and the ruthenium (II) and (III) complexes adopt the octahedral geometry, respectively. (Ekebergh, 2020).

For its part, $Ru_3(CO)_{12}$ cluster is known to catalyze a wide variety of reactions, such as hydroformylations, hydrogenations, hydrosilations, among others (Xion, 2017).

One of the advantages offered by this type of metal precursor is that it can be used in situ in the presence of different ligands, without the need to synthesize and isolate a complex, which means greater time and difficulty in its characterization. However, various authors have studied the chemical species that are formed from these reactions in situ and in general it has been shown that the ruthenium cluster maintains its structure without fragmenting, including the presence of metal-hydride and metal-carbon bonds. (Gazola, 2021)

On the other hand, the hydrogen transfer reaction, known as Meerwein-Ponndorf-Verlay (MPV) reduction, is applied in the pharmaceutical and fragrance industries. A problem with this reaction is that it requires the use of an aluminum alkoxide, which must be used in stoichiometric quantities, being a disadvantage for its application on an industrial scale. For this reason, interest has greatly increased in the hydrogen transfer reaction occurring catalytically, with transition metals such as Ir, Rh and Ru being those that have shown the best results. The catalysis has the potential to greatly enhance the sustainability of pharmaceutical products, leading to shorter and more efficient synthetic routes (Mannu, 2021).

In view of the above, are common metal-hydride bonds in hydrogen transfer reactions when 2-propanol is used as a hydrogen source and reaction medium, when the process taking place in a homogeneous phase.

For all the aforementioned, this article presents the synthesis of 1,8-naphthyridine derivatives and their potential application both as antimicrobial agents and as ligands for the hydrogen transfer reaction catalyzed by $Ru_3(CO)_{12.}$

## EXPERIMENTAL PROCEDURE

The proposed compounds were prepared in one pot synthetic step by Friedländer reaction between aromatic 2-aminoaldehyde (Majewicz, 1974) and active a-methyl ketones. NaOH promotes the condensation followed by cyclodehydration. When the reaction is performed using 2-aminonicotinaldehyde and *para* substituted-acetophenone, 2-phenyl-1,8-naphthyridine derivatives were obtained. Then, the heterocyclic compounds were tested as antimicrobial agents as well as catalyst precursor for transfer hydrogen reaction together to $Ru_3(CO)_{12}$.

### TYPICAL PROCEDURE 2-PHENYL-1,8-NAPHTHYRIDINE COMPOUNDS

Starting material 2-aminonicotinaldehyde (1,0 mmol) is added into 250 mL two-neck round-bottom flask equipped with a reflux condenser, containing ethanol (100 mL). Then, *para* substituted acetophenone (1,0 mmol) is added under nitrogen atmosphere. Saturated NaOH ethanolic solution is poured and the mixture has to be heated at reflux temperature during 4 h. The reaction progress is controlled by thin layer chromatography (TLC), using a dichloromethane:ethyl acetate (3:2) solvent system. The 2-phenyl-1,8-naphthyridine type compound is recovered by column chromatography or recrystallization depend on their solubility characteristics in ethanol media.

## AGAR DIFFUSION ASSAYS

Antimicrobial activity assays are performed with strains of gram negative *Escherichia coli* (*E. Coli* ATCC 25922 and clinical isolated); gram positive *Staphylococcus aureus* (*S. Aureus* ATCC 25923 and clinical isolated) and fungal *Candida albicans* (C. *parapsolosis* ATCC 22019); as reference for studies with *Candida* species.

The strains have to be cultivated and

keeping in nutrient agar (Becton Dickinson) as well as yeast strain in Sabouraud agar. Active cultives is prepared using a sterile loop to transfer microbial broth on nutrient agar plate (Becton Dickinson) for bacteria and Sabourand for yeast. Incubation time will be during 18 to 25 hours at 37 °C for bacteria and 24 to 30 hours for yeast.

This method is carried on for determination of antimicrobial activity of 2-phenyl-1,8-napthryidine compounds. It is taken 3 to 5 well isolated colonies care on morphology from nutrient agar for bacteria, be suspended into 0.85 % sterile saline solution (5 mL). The resultant suspension is stirred during 15 seconds and the equivalent cellular density adjust to 1,5 x $10^8$ cell/mL (equivalent to 0,5 McFarland) measure in a OXOID turbidimeter. For yeast the equivalent cellular density is adjusted 3.0 x $10^8$ cell/mL in a UV-VIS spectrophotometer at 520 nm.

Culture plates is inoculated on agar Mueller-Hinton (MH) for bacteria and MH agar 2.0 % glucose for yeast, antimicrobial compound solution (5 mL) is poured as 2.0 % dimethyl sulfoxide solution. Negative control will be DMSO and incubated at 37 °C during 18 to 24 h. Inhibition of bacteria and yeast growth is measured according to inhibition halo (mm) with a caliper. Analytical data for the synthesized compounds

## ASSAYS ON THE HYDROGEN TRANSFER REACTION

In a 250 mL two-neck round-bottom flask, under nitrogen, $Ru_3(CO)_{12}$ (8 mg; 0.0125 mmol), 2-phenyl-1,8-naphthyridine derivative (0.0375 mmol) and 2-propanol (4 mL) were added. The mixture was heated for 1 h to allow *in situ* formation of the catalyst. Subsequently, NaOH (4.75 mmol) was added and then acetophenone (150 mL, 1.28 mmol) as a substrate and *para*-cymene (300 mL) as an internal standard dissolved in a volume of 2-propanol to complete 10 mL of solution and in order to obtain a substrate:catalyst ratio of 103. On the contrary, to obtain a substrate:catalyst ratio of 205, double the amount of acetophenone was added, that is, (300 mL, 2.56 mmol).

## STUDY OF THE EFFECT OF THE CO ATMOSPHERE ON THE HYDROGEN TRANSFER REACTION

The *in situ* generation of the catalyst was carried out under a nitrogen atmosphere following the procedure described in the previous point. Subsequently, the nitrogen was replaced by a carbon monoxide, and then: NaOH (4.75 mmol) and immediately after acetophenone (300 mL, 2.56 mmol) and *para*-cymene (300 mL) dissolved in a volume of 2-propanol to complete 10 mL of solution.

## STUDY OF STRUCTURE-ACTIVITY RELATIONSHIPS IN THE HYDROGEN TRANSFER REACTION BY USING SUBSTITUTED ACETOPHENONE.

The same procedure described for a substrate:catalyst ratio of 205 was used, the compound 2-phenyl-1,8-naphthyridine was selected for the *in situ* generation of the catalyst with $Ru_3(CO)_{12}$. While acetophenone were tested and its *para*-substituted derivatives with the -Cl, -F, $-CH_3$ and $-OCH_3$ groups, respectively.

## RESULTS AND DISCUSSION

### ANALYTICAL DATA FOR THE SYNTHESIZED COMPOUNDS

2-PHENYL-1,8-NAPHTHYRIDINE (L1).

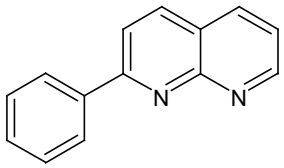

**Figure 1.** Structure of 2-phenyl-1,8-naphthyridine (L1).

White solid. Yield (77 %). $^1$H-NMR ($CDCl_3$, 400 MHz): δ 9.12 (dd, 1H, $H^7$, $^3J$ = 4.4 and $^4J$ = 1.8 Hz), 8.32 (m, 2H, $H^{12}$ and $H^{12'}$), 8.23 (d, 1H, $H^4$, $^3J$ = 8.5 Hz), 8.18 (dd, 1H, $H^5$, $^3J$ = 8.1 and $^4J$ = 1.8 Hz), 8.00 (d, 1H, $H^3$, $^3J$ = 8.5 Hz), 7.50 (m, 3H, $H^{13}$, $H^{13'}$ and $H^{14}$), 7.45 (dd, 1H, $H^6$, $^3J$ = 8.1 and $^3J$ = 4.4 Hz). Elemental analysis calculated for $C_{14}H_{10}N_2$; C (81.53 %), H (4.89 %), N (13.58 %). Found: C (81.61 %), H (4.79 %), N (13.49 %).

*2-[4-(MORFOLIN-4-YL)PHENYL]-1,8-NAPHTHYRIDINE (L2)*

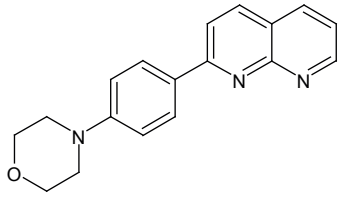

**Figure 2**. Structure of 2-[4-(morfolin-4-yl) phenyl]-1,8-naphthyridine (L2)

Yellow Solid. Yield (74 %). $^1$H-NMR ($CDCl_3$): δ 9.05 (dd, 1H, $H^7$, $^3J$ = 4.2 and $^4J$ = 1.8 Hz), 8.27 (d, 2H, $H^{12}$ and $H^{12'}$, $^3J$ = 9.0 Hz), 8.10 (m, 2H, $H^5$ and $H^4$), 7.91 (d, 1H, $H^3$, $^3J$ = 8.6 Hz), 7.37 (dd, 1H, $H^6$, $^3J$ = 8.0 and $^3J$ = 4.2 Hz), 6.99 (d, 2H, $H^{13}$ and $H^{13'}$, $^3J$ = 9.0 Hz), 3.85 (t, 4H, O-$CH_2$, $^3J$ = 4.8 Hz), 3.26 (t, 4H, N-$CH_2$, $^3J$ = 4.8 Hz). Elemental analysis calculated for $C_{18}H_{17}N_3O$; C (74.20 %), H (5.88 %), N (14.42 %). Found: C (74.03 %), H (6.02 %), N (14.22 %).

2-[4(1H-IMIDAZOL-1-YL-PHENYL)]-1,8-NAPHTHYRIDINE (L3)

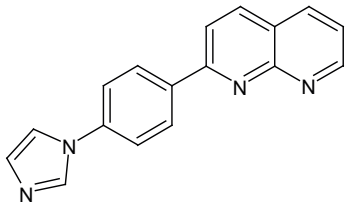

**Figure 3**. Structure of 2-[4(1*H*-imidazol-1-yl-phenyl)]-1,8-naphthyridine (L3).

White solid. Yield (92%). NMR-$^1$H ($CDCl_3$): δ 9.12 (dd, 1H, $H^7$, $^3J$ = 4.2 and $^4J$ = 1.9 Hz), 8.41 (d, 2H, $H^{12}$ and $H^{12'}$, $^3J$ = 8.5 Hz), 8.26 (d, 1H, $H^4$, $^3J$ = 8.5 Hz), 8.18 (dd, 1H, $H^5$, $^3J$ = 8.1 and $^4J$ = 1.9 Hz), 7.99 (d, 1H, $H^3$, $^3J$ = 8.5 Hz), 7.94 (s, 1H, $H^{16}$), 7.52 (d, 2H, $H^{13}$ and $H^{13'}$, $^3J$ = 8.5 Hz), 7.46 (dd, 1H, $H^6$, $^3J$ = 8.1 and $^3J$ = 4.2 Hz), 7.35 (s, 1H, $H^{18}$), 7.21 (s, 1H, $H^{19}$). Elemental analysis calculated for $C_{17}H_{12}N_4$; C (74.98 %), H (4.44 %), N (20.58 %). Found: C (74.57 %), H (4.89 %), N (20.74 %).

2-[(4-PIPERIDIN-1-YL)PHENYL]-1,8-NAPHTHYRIDINE (L4)

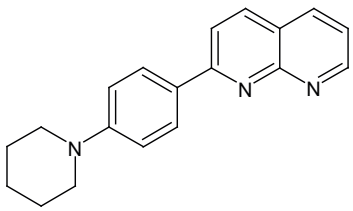

Figure 4. Structure of 2-[(4-piperidin-1-yl) phenyl]-1,8-naphthyridine (L4)

Red solid. Yield (85 %). $^1$H-NMR ($CDCl_3$): δ 9.06 (dd, 1H, $H^7$, $^3J$ = 4.4 and $^4J$ = 1.9 Hz), 8.24 (d, 2H, $H^{12}$ and $H^{12'}$, $^3J$ = 9.0 Hz), 8.11 (m, 2H, $H^4$ and $H^5$), 7.93 (d, 1H, $H^3$, $^3J$ = 8.6 Hz),

7.34 (dd, 1H, $H^6$, $^3J$ = 8.1 and $^3J$ = 4.4 Hz), 7.01 (d, 2H, $H^{13}$ and $H^{13'}$, $^3J$ = 9.0 Hz), 3.31 (t, 4H, N-$CH_2$, $^3J$ = 5.3 Hz), 1.71 (m, 4H, $CH_2$), 1.62 (m, 2H, $CH_2$). Elemental analysis calculated for $C_{19}H_{19}N_3$; C (78.86 %), H (6.62 %), N (14.52 %). Found: C (78.61 %), H (6.43 %), N 14.12 %).

## 2-(4'-TERT-BUTYL-2',6'-DIMETHYLPHENYL)-1,8 NAPHTHYRIDINE (L5)

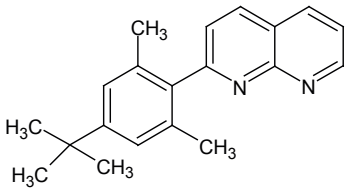


Figure 5. Structure of 2-(4'-tert-butyl-2',6'-dimethylphenyl)-1,8 naphthyridine (L5)

White solid. Yield (70 %). $^1$H-NMR ($CDCl_3$): δ 9.12 (dd, 1H, $H^7$, $^3J$ = 4.2 and $^4J$ = 1.8 Hz), 8.22 (m, 2H, $H^5$ and $H^4$), 7.47 (m, 2H, $H^3$ and $H^6$), 7.12 (s, 2H, $H^{13}$ and $H^{13'}$), 2.09 (s, 6H, -$CH_3$), 1.33 (s, 9H, $^t$Bu). Elemental analysis calculated for $C_{20}H_{22}N_2 \cdot 1.5H_2O$; C (75.68 %), H (7.94 %), N (8.83 %). Found: C (75.43 %), H (8.10 %), N (9.38 %).

A series of 2-phenyl-1,8-naphthyridine derivatives were synthesized from the condensation between 2-aminonicotinaldehyde and *para*-substituted acetophenones. The yields were between 70 and 92 %, all the compounds were solid and stable at room temperature.

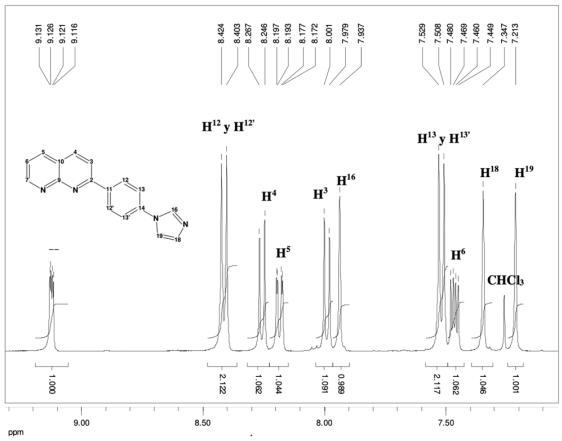


**Figure 6.** $^1$H-NMR ($CDCl_3$, 400 MHz) of compound L3.

In each case, the formation of 1,8-naphthyridine was confirmed by $^1$H-NMR spectroscopy, for example, the compound 3, its spectrum (figure 6) shown the characteristic signals of the 2-substituted 1,8-naphthyridine heterocycle. The proton $H^7$ appears of the form of a doublet-doublet consequence of two couplings with the protons $H^6$ and $H^5$, the values of the coupling constants found were $^3J$ = 4.2 and $^4J$ = 1.9 Hz with $H^6$ and $H^5$, respectively. The protons $H^4$ and $H^3$ appear as doublets coupling with each other, and the value of the coupling constant was found to be 8.5 Hz. Also, the protons of the *para*-substituted phenyl group, numbered as $H^{12}$ and $H^{12'}$; $H^{13}$ and $H^{13'}$ appear as doublets with a three-bond coupling constant of 8.5 Hz.

## RESULTS OF AGAR DIFFUSION ASSAYS

Firstly, compounds derived from 2-phenyl-1,8-naphthyridine were tested as antimicrobial agents against strains of *Candida albicans*, *Escherichia. coli* and *Staphylococcus aureus* which are microorganisms of hospital importance. Only L1 presented inhibition with a halo of 42 mm against a clinical isolate of *C. albicans* but this was not greater when the compound was evaluated with the antibiotic

ciprofloxacin. The other compounds from L2 to L5 did not inhibit the growth of the microorganisms tested.

## RESULTS OF THE HYDROGEN TRANSFER REACTION

Regarding the catalytic assays, in figure 7 is possible to see that the catalyst systems using compounds L1 to L4 shown conversion (%) of acetophenone to 1-phenylethanol close to 80% after 90 minutes of reaction. However, the system containing compound L5 does not exceed 30% of conversion in the same reaction time, having a similar behavior to compound $Ru_3(CO)_{12}$ by itself. This behavior could be explained due to the presence of bulky substituents in compound L5, which would prevent coordination with ruthenium. It could also be observed that in less than one hour of reaction, the system that presented the best results is that consisting of $Ru_3(CO)_{12}$ and the compound L1, that is, 2-phenyl-1,8-naphthyridine. For this reason, the following catalytic studies were carried out considering only the system made up of $Ru_3(CO)_{12}$ and L1. Complete results are summarized in the table 1.

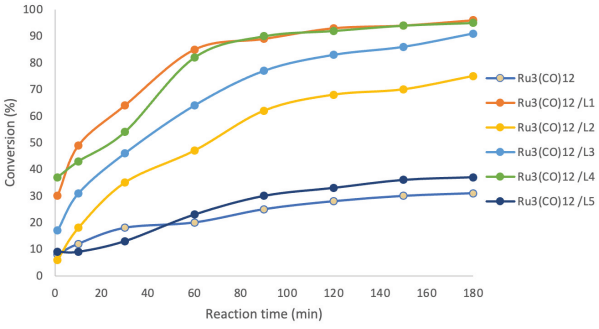


**Figure 7.** Conversion (%) of acetophenone to 1-phenylethanol for hydrogen transfer by using $Ru_3(CO)_{12}$ as catalyst and compounds L1 to L5. Substrate/catalyst ratio = 103/1.

| Reaction time (min) | Conversion (%) Under nitrogen ($N_2$) | Conversion (%) Under carbon monoxide (CO) |
|---|---|---|
| 0.5 | 25 | 24 |
| 1.5 | 27 | 25 |
| 5 | 43 | 25 |
| 10 | 54 | 27 |
| 25 | 74 | 50 |
| 50 | 80 | 63 |
| 90 | 86 | 77 |

**Table 2.** Conversion (%) of acetophenone to 1-phenylethanol for hydrogen transfer by using $Ru_3(CO)_{12}$ as catalyst and 2-phenyl-1,8-naphthyridine (L1). Under nitrogen and carbon monoxide (CO) atmosphere.

Substrate/catalyst ratio = 205/1

In order to obtain some information about mechanism of this reaction, it was increased substrate/catalyst ratio to 205/1 and the experiment was carried out under a nitrogen and the under a carbon monoxide atmosphere. It is well known that the compound $Ru_3(CO)_{12}$ contains CO ligands which can act as leaving group under certain conditions, therefore, the incorporation of carbon monoxide should influence the reaction.

The results of both experiments are shown in table 2, which served to construct the curves in figure 7, it can be seen that in the first minutes of the reaction, the presence of carbon monoxide causes the conversion of acetophenone to 1-phenylethanol to significantly decrease. However, it does not inhibit it, what indicates that it would only be hindering the formation of vacant sites in the catalyst and that the function of CO would effectively be a leaving group.

| Reaction time (min) | $Ru_3(CO)_{12}$ (%) | $Ru_3(CO)_{12}$/L1 (%) | $Ru_3(CO)_{12}$/L2 (%) | $Ru_3(CO)_{12}$/L3 (%) | $Ru_3(CO)_{12}$/L4 (%) | $Ru_3(CO)_{12}$/L5 (%) |
|---|---|---|---|---|---|---|
| 1 | 8 | 30 | 6 | 17 | 37 | 9 |
| 10 | 12 | 49 | 18 | 31 | 43 | 9 |
| 30 | 18 | 64 | 35 | 46 | 54 | 13 |
| 60 | 20 | 85 | 47 | 64 | 82 | 23 |
| 90 | 25 | 89 | 62 | 77 | 90 | 30 |
| 120 | 28 | 93 | 68 | 83 | 92 | 33 |
| 150 | 30 | 94 | 70 | 86 | 94 | 36 |
| 180 | 31 | 96 | 75 | 91 | 95 | 37 |

**Table 1.** Conversion (%) of acetophenone to 1-phenylethanol for hydrogen transfer by using $Ru_3(CO)_{12}$ as catalyst and compounds L1 to L5.

Substrate/catalyst ratio = 103/1.

| Reaction time (min) | TOF ($h^{-1}$) X = -Cl | TOF ($h^{-1}$) X = -F | TOF ($h^{-1}$) X = -H | TOF ($h^{-1}$) X = $-CH_3$ | TOF ($h^{-1}$) X = $-OCH_3$ |
|---|---|---|---|---|---|
| 0.5 | 7661 | 6178 | 6178 | 4943 | 4943 |
| 1.5 | 2708 | 2297 | 2215 | 1887 | 1723 |
| 5 | 1087 | 1063 | 1063 | 816 | 618 |
| 10 | 688 | 676 | 652 | 483 | 374 |
| 25 | 389 | 374 | 364 | 290 | 192 |
| 50 | 220 | 203 | 198 | 180 | 129 |
| 90 | 124 | 123 | 118 | 109 | 85 |

**Table 3.** Turnover frequency (TOF) measured for hydrogen transfer reaction of acetophenone

Substrate/catalyst ratio = 205/1.

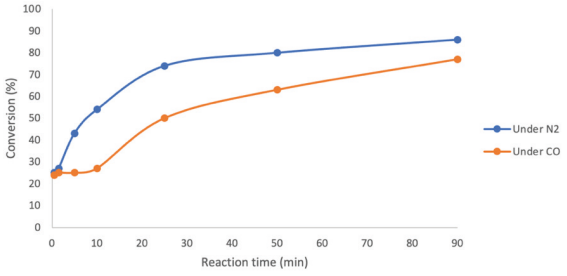


**Figure 8.** Conversion (%) of acetophenone to 1-phenylethanol for hydrogen transfer by using $Ru_3(CO)_{12}$ as catalyst and compound L1. Under nitrogen and carbon monoxide atmosphere. Substrate/catalyst ratio = 205/1.

Based on the previous results, it can be assumed that the catalyst formed in situ between $Ru_3(CO)_{12}$ and 2-phenyl-1,8-naphthyridine (L1) contains the heterocyclic compound bonded to ruthenium and is bonded to carbon monoxide molecules as well. In order to obtain more information about the chemical species formed in situ, $Ru_3(CO)_{12}$ (0.47 mmol; 300 mg) and 2-phenyl-1,8-naphthyridine (1.45 mmol; 300 mg) were added to a 250 mL two-neck round-bottom flask and 2-propanol, until completing a volume of 100 mL. The mixture was heated for 30 minutes and after that time a dark-colored solution was obtained, which was evaporated to dryness and the residue purified by silica gel column chromatography, eluting with a mixture of dichloromethane: *n*-hexane = 1:1. The isolated compound by evaporation of the solvent was a red solid. The structure of the new ruthenium complex was determined by X-ray crystallography of a single crystal. This corresponds to a trimetallic ruthenium cluster with a triangular geometry, the Ru-Ru distances were between 2.85 and 2.94 Å in length. These values are in agreement

with those reported in the literature for other trimetallic ruthenium clusters, for example, the complex obtained by reacting $Ru_3(CO)_{12}$ with 6,6'-dimethyl-2,2'-bipyridine shown a similar structure, with Ru-Ru bond lengths between 2.74 and 2.96 Å (Cabeza, 2006). The two hydride bridging atoms could not be located exactly due to the thermal agitation of the molecule and its small electron density, so they were placed using theoretical methods. In any case, its presence had been clearly demonstrated by proton nuclear magnetic resonance at δ -12.2 and -12.8 (Vásquez-García, 2009), respectively (figure 9).

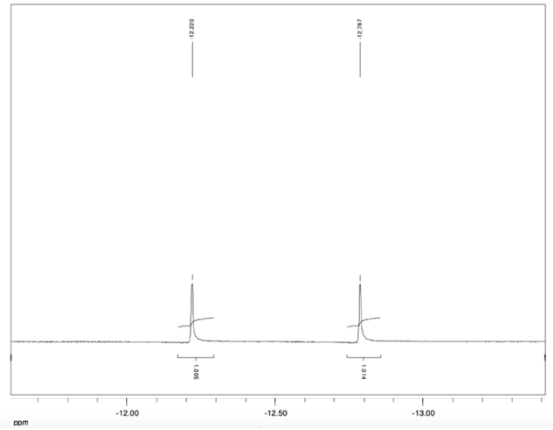


**Figure 9.** $^1$H-NMR ($CDCl_3$, 400 MHz) of compound formed by reacting $Ru_3(CO)_{12}$ and 2-phenyl-1,8-naphtyridine. (Between -11.5 to -13.5 ppm).

Perhaps the most striking thing about this structure is the presence of two 2-phenyl-1,8-naphthridine (L1) acting as a bridge ligand between Ru(1) and Ru(2), and Ru(1) and Ru(3), respectively. The activation of an aromatic C($sp^2$)-H bond is evident through the oxidative addition of the L1 compound. This type of activation is known as cyclometallation (Oi, 2008), since a cycle is formed in which there is a metal-carbon bond. The coordination of L1 to a ruthenium atom decreases the activation energy for breaking the C-H bond of the ligand, which makes the process more favorable from an energetic point of view (Cabeza, 2010). It believes that, the transition state for this activation must also contain coordinating the L1 ligand with a ruthenium atom. The rest of the coordination sites are completed with eight carbon monoxide molecules coordinated as terminal carbonyls. In relation to the above, it was registered an infrared ($CH_2Cl_2$) spectrum of this compound showed three strong coordinated carbon monoxide stretching bands at 2061, 2025 and 2000 $cm^{-1}$, being consistent with those found in the molecular structure determined by X-ray crystallography (figure 10). Furthermore, the oxidation state (0) of ruthenium in $Ru_3(CO)_{12}$ allows this complex to transfer a pair of electrons to the compound L1, causing the oxidative addition of the C-H bond. The hydrogen that is added in this case was a metal-hydride. Although there are other examples of cyclometalation in which the metal is in a high oxidation state, being poor in electrons.

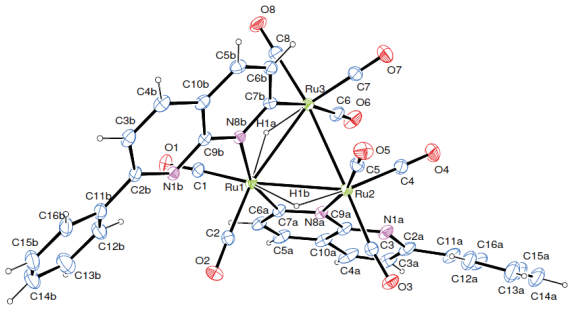


**Figure 10.** Molecular view of the complex formed by reacting $Ru_3(CO)_{12}$ and 2-phenyl-1,8-naphthyridine.

Finally, structure-activity relationships were studied on the hydrogen transfer reaction of acetophenone to 1-phenylethanol. The experimental data were recorded at 90 seconds (1.5 min) of reaction, calculating the value of the TOF repetition frequency and plotted a graph of TOF (initial) against the constants of Hammett of *para*-substituted (σp) aromatic systems (Carey, 2007).

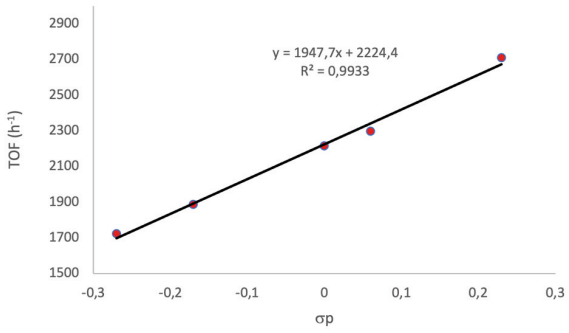


**Figure 11.** Initial catalytic activity (TOF) against Hammett's constant for para-substituted aromatic systems.

The linear relationship found in the graph of figure 11 confirms that for the entire series of *para*-substituted substrates the conversion to 1-phenylethanol follows a common mechanism, and the positive slope means that the introduction of electron-withdrawing groups such as -Cl and -F on the benzene ring increases the catalytic activity in the reduction of acetophenone. That is, in the transition state, an increase in negative charge occurs in the reaction center, in this case the carbonyl carbon of acetophenone. These results indicate that the rate-limiting step of the reaction depends on the electronic density of the carbonyl group of acetophenone, that is, decrease the electronic density on this carbon. This is a clear indication that the rate-limiting step of the reaction is a nucleophilic attack on the carbonyl carbon of acetophenone, and the attacking nucleophile is naturally the hydride bonded of the cluster complex.

## CONCLUSION

In relation to the activity of 1,8-naphthyridine derivatives as antimicrobial agents, they require further research. However, preliminary results could be related to the ability of these compounds to bind with DNA gyrase and their lipophilicity.

For their part, the catalytic assays of the hydrogen transfer reaction of acetophenone shown evidence that the active species in this process involved metal hydrides and that ruthenium cluster maintains its structure, being stabilized by the compounds L1 to L4 when act as ligands. Furthermore, the reaction mechanism involves metal hydride attack on the carbonyl of acetophenone as a rate-limiting step of the reaction.

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15. The molecular structure of the complex was determined in a single crystal diffractometer with Smart APEX area detector. Selected data: Formula: $C_{36}H_{18}N_4O_8Ru_3 \cdot 0.25(CHCl_3)$, space group: $P_{-1}$, crystal system: triclinic, unit cell lengths (Å): a = 9.0230(13); b = 13.514(2); c = 16.996(3), unit cell angles (°): a = 68.671(2); b = 77,100(2); g = 87,737(2).

16. The products obtained from the catalytic tests were analyzed using an Agilent 6890 series gas chromatograph, with a flame ionization detector and an HP-INNOWAX column (30 m x 0.248 mm x 0.25 mm). Operating temperature range between 40 and 260 °C.