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Research Article

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Synthesis and Characterization of N-Heterocyclic Carbene and their Complexes with Ni (II) and Studying their Biological Activity against *Escherichia coli*

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ABSTRACT

For the evaluation of binding and catalytic nature of N-heterocyclic carbenes (NHCs) and their complexes, New imidazolium salts (DII, DTI) and N-heterocyclic carbine complexes were designed (Ni-NHC), synthesized and structurally characterized by NMR (^{1}H,^{13}C), IR, and other methods. Where the studying showed that the ligands and their complexes have a biological effect against E.coli.

Keywords: N-Heterocyclic carbene; Ni-NHC complexes; Imidazole

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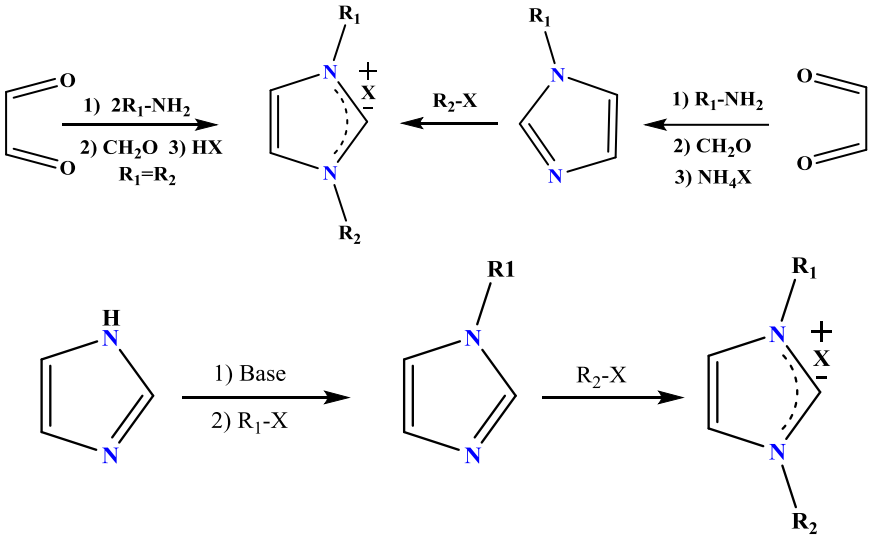
INTRODUCTION

The first stable N-heterocyclic carbene reported by Arduengo et al. [1] triggered the development of stable singlet carbenes from laboratory interests to key compounds for manifold applications, particularly in catalysis.

N-heterocyclic carbenes (NHCs) have been embraced as spectator ligands in catalyst design with a remarkable speed in past few decades. Due to the strong metal carbon bond, carbene complexes give robust catalytic systems and so, a number of transition metal complexes of multidentate NHCs containing phosphorous, oxygen, and nitrogen functionalities have been reported. Such ligands may significantly improve catalyst .stability and their potential hemilability provide ease of generation of vacant coordination site and catalytically active species [2-4]. He first catalytic application of NHCs in transition-metal catalysis was reported by Herrmann who realized the great potential of NHCs as ancillary ligands in nickel mediated cross-coupling reactions and in ruthenium mediated olefin metathesis. Nowadays, NHC-metal complexes have found wide applications in hydrogen transfer reactions and hydrosilylation reactions, especially C-C and C-N coupling reactions. Especially, the NHC ligands bearing hemilabile donor functionalities like nitrogen, oxygen or sulfur allow efficient stabilization of the catalytic species, while rapidly opening the free coordination sites for incoming substrates [5-7].

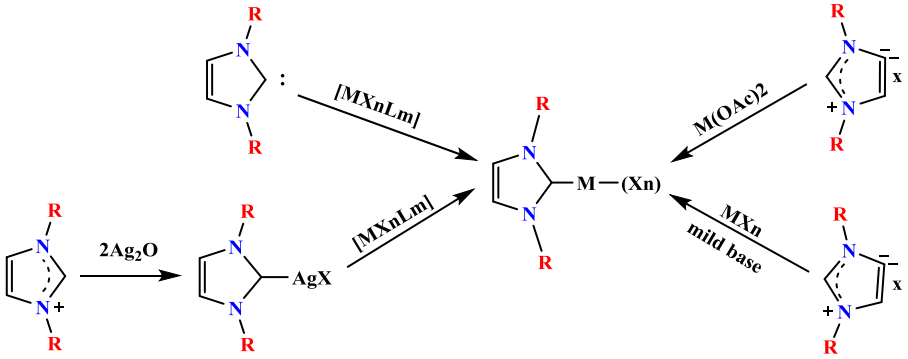
Further, the transition-metal-catalyzed amination of aryl halides has become one of the most powerful methods to construct arylamines. Most studies have focused on palladium and copper complexes as catalysts. However, the development of a general, robust and operationally simple catalytic system of Ni catalyzed C−N cross-coupling reactions has remained significantly challenging [8-10]. Many groups have expanded Ni-catalyzed C−N cross-coupling to include new electrophiles such as aryl, sulfamates, methyl ethers, phosphates, pivalates, and nitriles. In 2007, Yang reported the first use of NHC complexes of the type $(Ph3P)_2Ni(1\text{-nap})Cl$ used in C-N coupling reactions All of these methods have their own advantages [11-13].

Hence, the development of stable catalytic system with NHC-Ni(II) catalysts those can be performed under mild conditions has received much attention, NHCs are usually prepared by the deprotonation of imidazolium salts, therefore first of all it is necessary to synthesize the appropriate substituted pro-ligands. An NHC precursor can be prepared using several methods [14].



Scheme 1. Different ways to synthesis an imidazolium salts

Today, transition metal complexes of NHCs are mainly formed using four methods [14]:



Scheme 2. Four general methods to synthesize NHC-M complexes

Imidazolium units can thus be considered as privileged structural motifs for the conception and design of specifically tailored charged systems in a lot of these fields dedicated to research and development [15]:

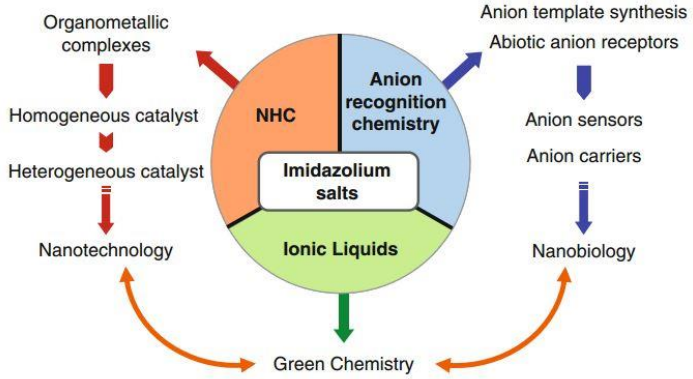


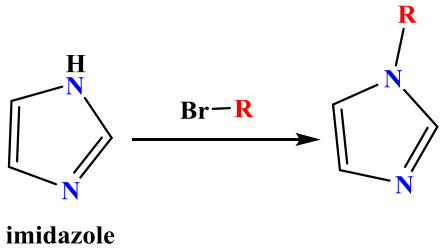
Figure 1. The imidazolium pool at the crossroads of multidisciplinary fields in chemistry

Apparatus

All reactions for the preparation of imidazolium salts and NHC-Nickel complexes were carried out under argon in flame-dried glassware using standard Schlenk techniques. Nuclear magnetic resonance spectra were recorded on Bruker 400 MHz spectrometers at ambient temperature. ^{1}H and ^{13}C NMR peaks are labelled as singlet (s), doublet (d), triplet (t), and multiplet (m), chemical shifts were referenced with respect to solvent signals. FT-IR spectra were recorded on shimadzu (Schemes 1-4).

General Methods for Synthesis of Alkyl-imidazole

Alkyl-imidazole was prepared by added bromo alkane (1mmol), imidazole (1 mmol), 30 ml methanol, K_2CO_3 (1 mmol), and anhydrous $CuSO_4$ (0.001 g) were mixed and heated at 90°C under argon for 5 h. After cooling to RT, the resultant solid was extracted with a mixture of MeOH/$CHCl_3$ (2x40 mL). The white solid was filtered and washed with water and a mixture of THF/Et_2O.

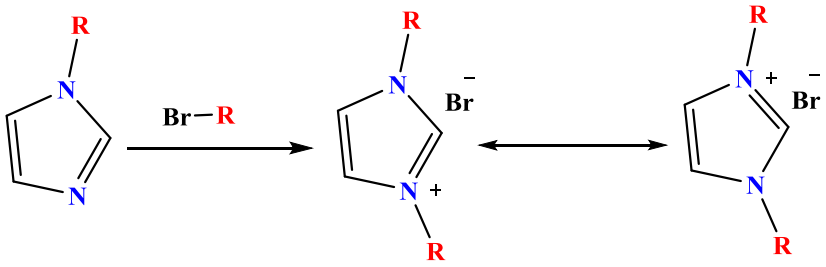


II ***R= propane*, TI *R= isobutane***

Scheme 3. Preparation of Alkyl-imidazole

General Procedure for Synthesis of 1,3-Dialkylimidazole Salts

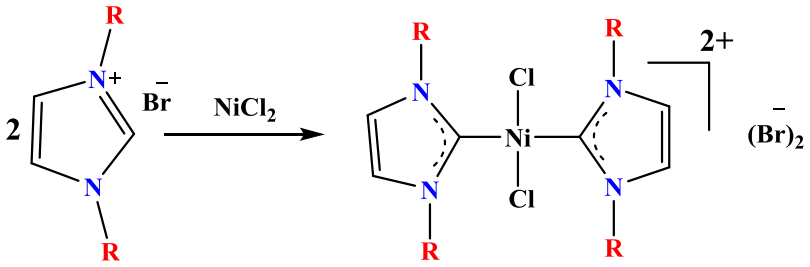
Alkyl-imidazole (1.5 mmol) and bromo alkane (1.5 mmol) were stirred in dioxane (40 mL) at 85°C for 24h. After cooling to RT, the desired white/yellow precipitate was filtered off and dried under vacuum.



Scheme 4. Preparation of 1,3-dialkylimidazole salts

General Method for the Preparation of the NHC-Nickel Complexes

A stirred DMSO solution (5 mL) of $NiCl_2$ (17.733 mg, 0.1 mmol) and imidazolium salts (0.2 mmol) was heated to 90°C for 24 h, K_2CO_3 (0.15 mmol) was added. After vigorous mixing, the precipitates were collected. Diethyl ether was added and the solid collected, washed with diethyl ether and air-dried (Figure 1).



Scheme 5. Preparation of NHC-Nickel complexes

1-isopropyl-1H-imidazole (II): Yield 0.17 g (77.27%). FT-IR(KBr): υ(cm^{-1}); 3425(C_{aliph}-$N_{imidazol}$),3118(C-H_{aliph}),1651(C=$N_{imidazol}$),1500(C_{arom}-$N_{imidazol}$), 1327(C_{aliph}-$N_{imidazol}$) ^{13}C NMR (400MHz, DMSO-d6) δ 138.96 , 132.49 , 126.24 , 51.30 , 22.05 .

1,3-diisopropyl-1H-imidazolium (DII): White powder. Yield 0.399 g (69.08%), mp: 185-187ºC. FT-IR(KBr): υ(cm^{-1}); 3421(C_{aliph}-$N_{imidazol}$), 3134(C-H_{arom}),2983(C-H_{aliph}),1631(C=$N_{imidazol}$),1554(C_{arom}-$N_{imidazol}$), 1467(C_{aliph}-$N_{imidazol}$).**^{1}H NMR** (400 MHz, DMSO-d6) δ 9.60 (t, J=1.8 Hz, 1H), 7.99 (d, J=1.6 Hz, 1H), 5.02 – 4.15 (m, 1H), 1.48 (d, J=6.7 Hz, 6H).**^{13}C NMR** (400 MHz, DMSO-d6) δ 134.28 , 121.11 , 52.68 , 22.84 .

1-(tert-butyl)-1H-imidazole(TI): Yield 0.200 g (70.21%), **FT-IR(KBr):** υ(cm^{-1})**;** 3406(C_{aliph}-$N_{imidazol}$),3111(C-H_{arom}),2960(C-H_{aliph}),1668(C=$N_{imidazol}$),1510(C_{arom}-$N_{imidazol}$), 1462(C_{aliph}-$N_{imidazol}$) **^{13}C NMR** (400 MHz, DMSO-d_6) δ 135.75 , 118.04 , 107.68 , 58.43 , 29.69.

1,3-di-tert-butyl-1H-imidazolium(DTI): White powder. Yield 0.310 g (51.62%), mp: 199-200ºC **FT-IR(KBr):** υ(cm^{-1})**;** 3442(C_{aliph}-$N_{imidazol}$),3055(C-H_{arom}),2980(C-H_{aliph}),1631(C=$N_{imidazol}$),1546(C_{arom}-$N_{imidazol}$), 1471(C_{aliph}-$N_{imidazol}$).**^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 4.24 (s, 1H), 2.51 (s, 3H).**^{13}C NMR** (400 MHz, DMSO-d_6) δ 133.22 , 121.56 , 60.82 , 30.04 .

bis(1,3- diisopropyl imidazolium)Nickel(II) chloride[Ni(DII)$_2$Cl$_2$)]Br$^-_2$:

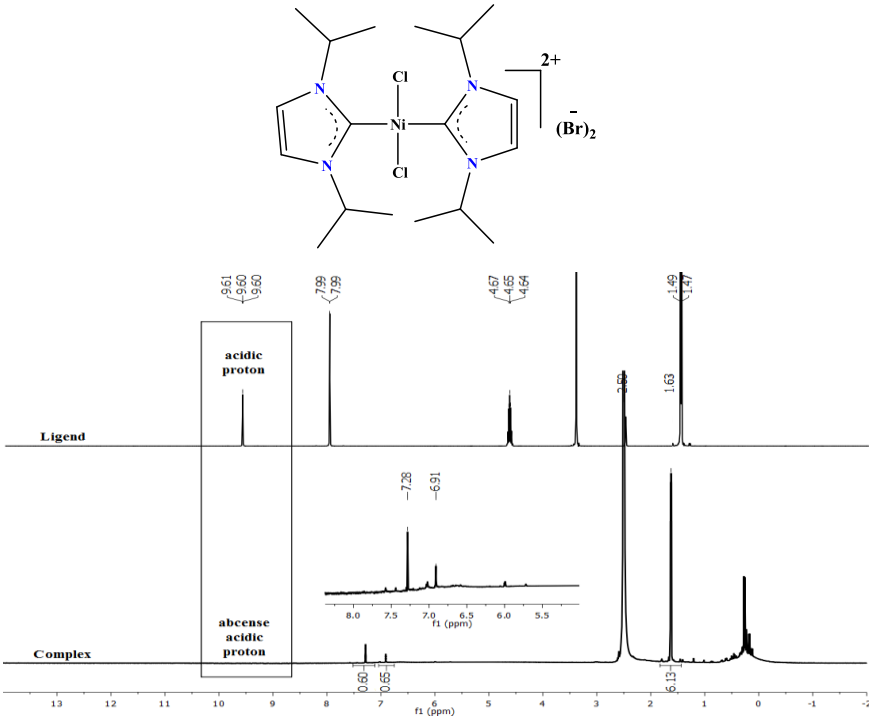


Figure 2. ^{1}H NMR for (DII & [Ni(DII)$_2$Cl$_2$)]Br$^-_2$

Brown powder. Yield 0.0249 g (59.42%), mp: 360-362ºC. **FT-IR(KBr):** υ(cm^{-1})**;** 3442(C_{aliph}-$N_{imidazol}$),3049(C-H_{arom}),2858,2931(C-H_{aliph}), 1625(C=$N_{imidazol}$),1546(C_{arom}-$N_{imidazol}$), 1454(C_{aliph}-$N_{imidazol}$)**.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (s, 1H), 7.02 (s, 1H), 1.73 (dd, *J*=53.1, 2.5 Hz, 6H) (Figure 2).

bis(1,3- di-tert-butyl imidazolium)Nickel(II) chloride[Ni(DTI)$_2$Cl$_2$)]Br$^-_2$:

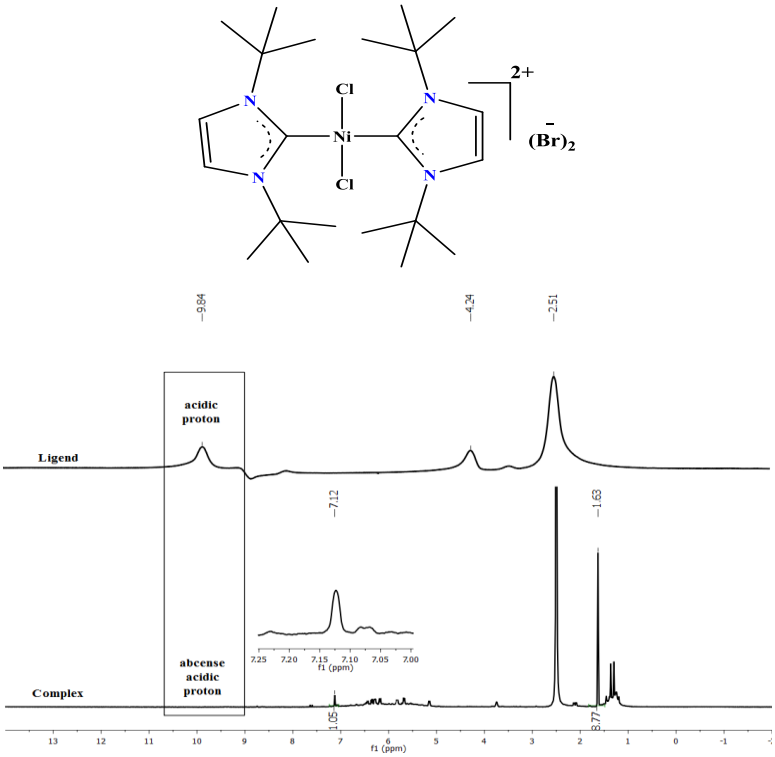


Figure 3. ^{1}H NMR for (DTI & $[Ni(DTI)_2Cl_2)]Br^-_2$

Brown powder. Yield 0.0201g (56.14%),mp:> 360 ºC. **FT-IR(KBr):** υ(cm^{-1})**;** 3363(C_{aliph}-$N_{imidazol}$),3045(C-H_{arom}),2920 (C-H_{aliph}), 1637(C=$N_{imidazol}$),1565(C_{arom}-$N_{imidazol}$), 1500(C_{aliph}-$N_{imidazol}$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 (s, 1H), 1.63 (s, 9H) (Figure 3).

Determine the Metal Content of the Complexes $[Ni(DII)_2Cl_2)]Br^-_2$

$$[Ni(DII)_2Cl_2]Br^-_2 + 2HNO_3 \longrightarrow NiO + 2HBr + 2DII + Cl_2 + O_2$$

643.63g/mol 74.69g/mol

0.022g Xg

X= 0.0027g (NiO .....calculated)

The actual rate is determined by taking 0.022g of the complex in a melting-pot and diluting the compound with concentrated nitric acid and put it in the cauldron at 800 ° C for three hours,
The weight of the output was 0.0022g, which is the actual rate of the nickel(II) oxide in the complex.
In a similar way, we determined the metal content of the complex $[Ni(DTI)_2Cl_2)]Br^-_2$where we obtained the results:

Table 1. the metal content of the complexes $[Ni(DII)_2Cl_2)]Br^-_2$ & $[Ni(DTI)_2Cl_2)]Br^-_2$

complex	NiO%		Ni%	
	(found)	(cal)	(found)	(cal)
$[Ni(DII)_2Cl_2)]Br^-_2$	10.90	12.27	8.18	9.54

$[Ni(DTI)_2Cl_2)]Br^-_2$	9.54	11.36	7.27	8.63

Antimicrobial Properties of Nickel(II) -NHC Complexes

The antimicrobial activity was reported in terms of the minimum inhibitory concentration (MIC) values, which are defined as the lowest concentration of an antimicrobial that visibly inhibits the growth of the bacteria after an overnight incubation.

Minimal inhibitory concentrations for each compound were investigated against Escherichia coli .The test organism was laboratory strains used to test a range of concentration of the nickel compounds for minimum inhibitory concentration determination. Antimicrobial activities of the nickel(II) -NHC complexes were determined by using agar dilution procedure and were tested with different concentrations of the compounds. The minimum inhibitory concentration (MIC) of synthesized Nickel complexes against Gram positive, Gram negative bacteria and fungus are summarized in Table 1. Gentomycin as standard drugs for comparison.

As shown in the table, antimicrobial activity against Escherichia coli was observed in the ligands their complexes tested at 50,100 µg/mL concentrations (Figure 4):

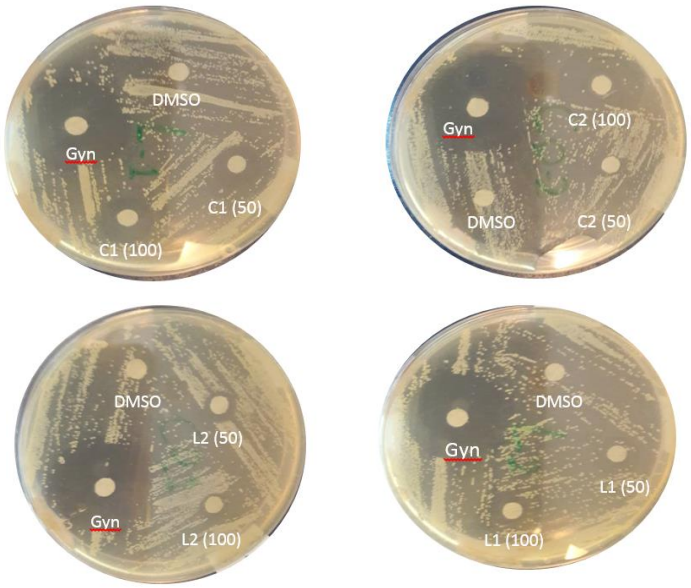


Figure 4. Antimicrobial activity against Escherichia coli was observed in the ligands their complexes tested at 50,100 µg/mL concentrations

Table 2. Demonstrates the results of the biological study obtained for the prepared compounds

Compound	(C µg/ml)	Diameter inhibition (mm)	(C µg/ml)	Diameter inhibition (mm)	Diameter inhibition (mm) standard drugs
DII(L1)	100	20	50	15	27
DTI(L2)	100	16	50	14	28
$[Ni(DII)_2Cl_2)]Br^-_2$ (C1)	100	20	50	19	28
$[Ni(DTI)_2Cl_2)]Br^-_2$ (C2)	100	21	50	7	28

RESULTS AND DISCUSSION

Imidazolium salts can be obtained from Alkyl-imidazole by stepwise aryl-/alkylation. Firstly, we prepared Alkyl-imidazole by reaction of bromo alkane with imidazole(Scheme 3), in the presence of K2CO3 and anhydrous

$CuSO_4$. The imidazolium salt can be obtained by refluxing Alkyl-imidazole with bromo alkane (Schemes 4 and 5). Both compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR.
For Alkyl-imidazole and imidazolium salts (II, TI, DII,DTI) strong and sharp stretching vibrations (3425, 3406, 3421 , 3442, cm^{-1}) appeared for tertiary nitrogens of imidazolium ring (C_{aliph}–$N_{imidazol}$).
NMR spectra of all the compounds were analyzed in DMSO -d6 over the scan range 0 to 15δ ppm for ^{1}H NMR and 0 to 210 δ ppm for ^{13}C NMR studies. In the ^{1}H NMR spectra, a characteristic sharp singlet (Ha) for imidazolium salts for acidic proton (NCHN) indicated the successful formation of target ligands (DII,DTI) [16]. Similarly, the structural features of the salts were further confirmed by the ^{13}C NMR data. In ^{13}C NMR spectra, the chemical shift values of (NCN) were observed within the range δ133.22 –134.28 ppm which is also in agreement with reported data for similar azolium salts. Synthesis of Ni–NHC complexes was confirmed by the disappearance of acidic proton peak (Ha) in ^{1}H NMR spectrum for $[Ni(DII)_2Cl_2)]Br_{-2}$ & $[Ni(DTI)_2Cl_2)]Br_{-2}$ [16,17].

CONCLUSION

In conclusion, four new compounds (NHC precursors, Ni-NHC complexes) based on imidazole were synthesized and fully characterized by NMR(1H,13C), IR. By means of imidazole ring, N-Heterocyclic Carbene and ionic liqud were synthesized. Through these compounds, organometallic complexes of nickel were synthesized; Carbon is associated with a sigma bond with the metal. Where the study showed that the ligands and their complexes have a biological effect.

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