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Review

Synthesis and applications: Ten years of experience in monodentate, bidentate, tridentate and macrocycle pyrazole heterocyclic chemistry

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Herein we report the development of efficient methods to prepare monodentate, bidentate, tridentate and macrocycle compounds based on pyrazole moieties, with the opportunity to change easily structure, substituents, cavities or all these parameters in the synthesis of huge library compounds. These methods take advantage of the vast number of commercially available starting materials containing functional and aliphatic or aromatic amines. Such as structural and electronic diversity makes these approaches well suited to the production of large arrays of compounds for potential application in medicinal, corrosion or coordination chemistry.

Key words: Pyrazole, bipyrazole, bis pyrazole, N-donor electron rich, macrocycle.

INTRODUCTION

The chemistry of nitrogen containing multipodal molecules is attracting current interest in the scientific world due to their specificity for biological targets (Kaim and Schwederski, 2006). These compounds are also of great importance for building polynuclear complexes (Bouwman et al., 1990) as models for bioinorganic systems (Chen et al., 1991; Pate et al., 1987; Nelson et al., 1983; Mukherjee, 2000; Pons et al., 2001) as well as for the discovery of new catalyst precursors (Sorrell et al., 1984). The pyrazol ring seems to play a key role as it is involved in several types of chelating ligands (Sorrell et al., 1987; Sorrell et al., 1991), which were used in models that mimic active sites of copper proteins (Paul et al., 1991; Ross and Solomon, 1991; Thulke-Gross et al., 1998). Meanwhile, the searches concerning the properties of the nitrogen ligand complexes increased in an exponential way (Kalynasundaram, 1982; Tarrago et al., 1991; Gross et al., 2009), largely because of their possible use as photo-catalysts during the conversion of the solar energy (Kober et al., 1980; Tarrago et al., 1990).

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Specially the 2,2'-bipyridine disubstitued (Juris et al., 1988), the 2,2 '-biquinoline (Barigelletti et al., 1983), the 2,2'-bipyrazine (Casper and Meyer, 1983) and the 2,2 '-bipyrimidine (Thummel, 1991). Relatively few authors were interested in the synthesis of another different bidentate ligand to the 2,2 '-bipyridine and its analogues, such as bipyrazole ligands. During last few decades many pyrazole and triazole derivatives have been synthesized for biological, medical and industrial purposes. These heterocyclic compounds have been proven to be useful as potential anti-inflammatory agents (Bruno et al., 1999), cytotoxic agents (Kumar et al., 1994), insecticides (Chou et al., 2007), herbicides (Schnatterer et al., 1996), fungicides (Jensen-Korte et al., 1986) and in the synthesis of heat resistant polymers (Kim et al., 2009). In this review, we summarise our contribution in this field during ten years of working in this topic by the synthesis of some new materials based on heterocyclic chemistry especially pyrazole, in different form like having just one pyrazole unit, two pyrazolic units system having an amine in the middle, two heterocyclic systems are connected without junction between them and macrocycle pyrazolic moieties. These compounds open many and diverse applications such as corrosion, biological, catalysis and theoretical studies, these purpose will be highlight too in

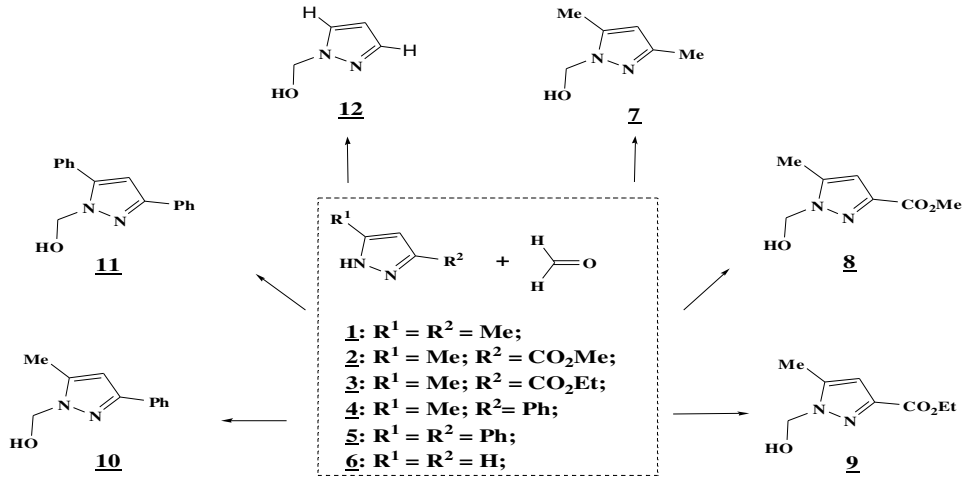


Figure 1. Synthesis of divers monodentate compounds based on pyrazole.

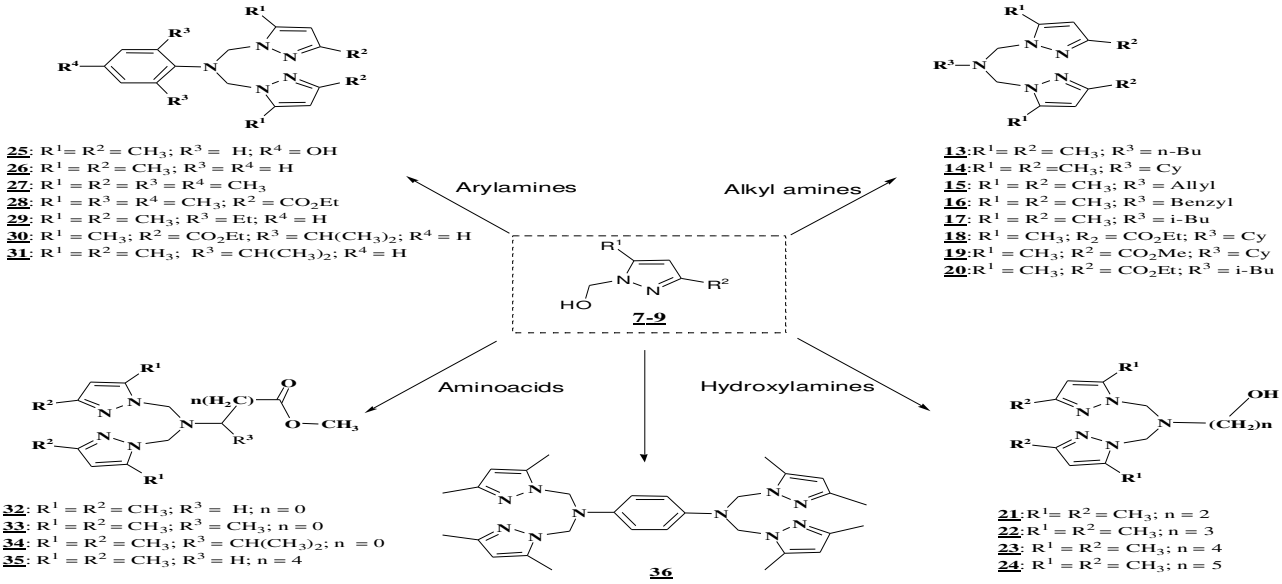


Figure 2. General scheme for the condensation of hydroxymethypyrazole and amines.

this review.

SYNTHESIS OF NITROGEN ELECTRON RICH MATERIALS BASED ON PYRAZOLE

Synthesis of heterocycle having one pyrazole moieties

The first step in our synthesis methodologies is the preparation of hydroxymethyl heterocycle by condensation of pyrazole 1-6 (Lupo et al., 1984; Ramdani and Tarrago, 1981) by hydroxylation of pyrazole, and their disubstituted derivatives, with formaldehyde to afford the other reagents 7-12 with good yields (Dvoretzky and Richter, 1950) (Figure 1).

Synthesis of N,N-bis(pyrazol-1-ylmethyl)amine derivatives

To achieve these compounds, we used different strategies; by condensation of two equivalent of hydroxymethyl substituted pyrazole 7-9 with one equivalent of amines, using three synthesis methodologies, such as microwave conditions (without solvent during 20 min), or heating at 60°C for 4 h or by stirring for 4 days at 25°C in the presence of acetonitrile as solvent. We got a huge and divers library of compounds with R^3 as alkyl group 13-20 (Touzani et al., 2001a), hydroxyl group 21-24 (El Kodadi et al., 2008; El Kodadi et al., 2003), bulky group 25-31 (Garbacia et al., 2005), amino acid derivatives 32-35 (Boussalah et al., 2009) and bis tridentate 36 (Bouabdallah et al., 2007a) (Figure 2).

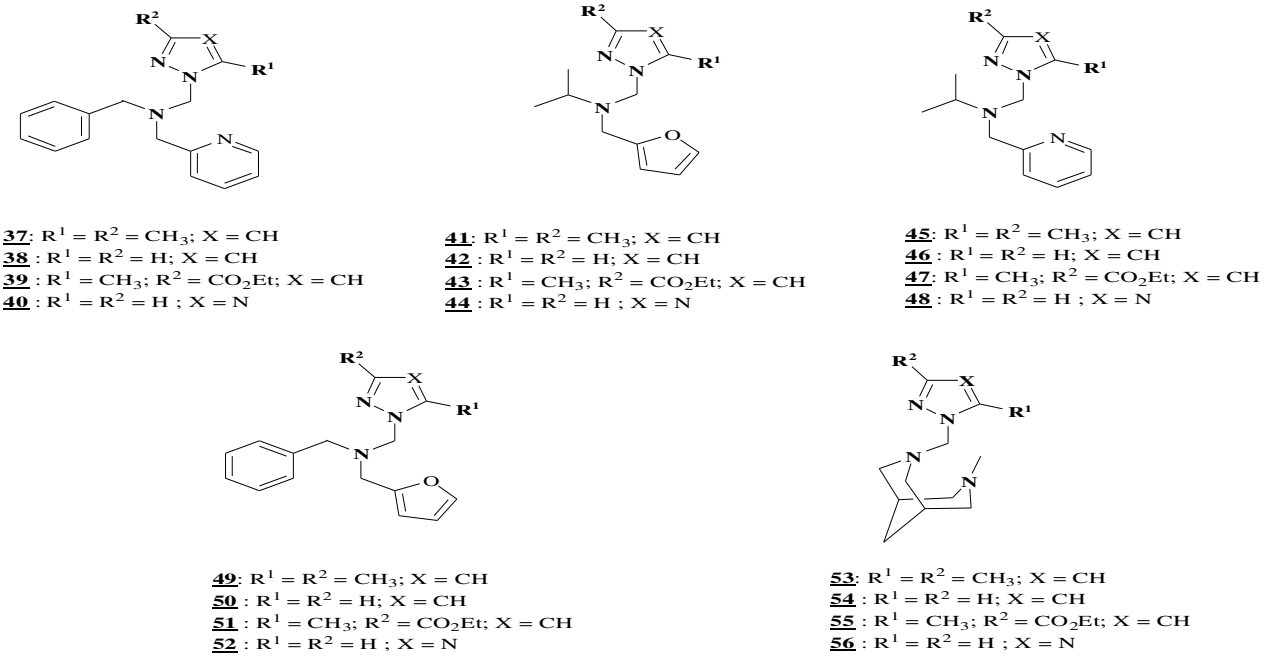


Figure 3. Library of compounds prepared with good and excellent yields.

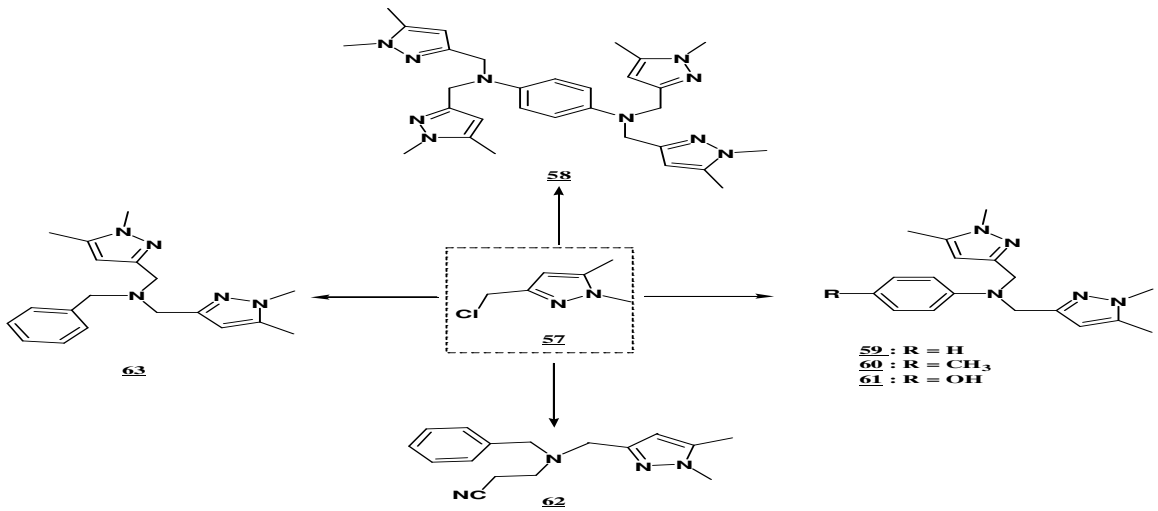


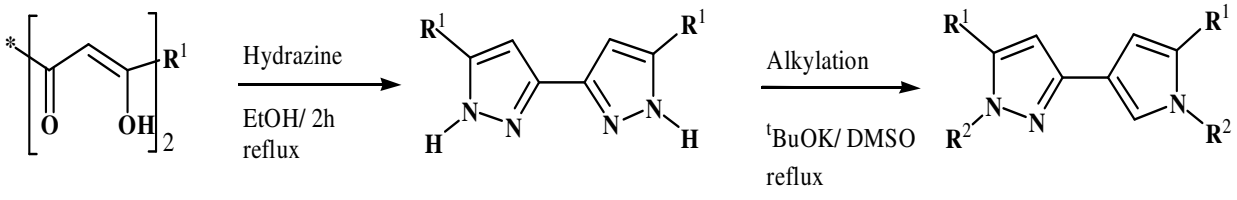
Figure 4. Compounds with NCC junction between the pyrazole and the amino group.

Synthesis of N,N-bis(heterocycl-1-ylmethyl)amine mixed derivatives based on pyrazole and triazole

We have developed an efficient access to tripodal compounds with the opportunity to change easily one, two, or all three of the building blocks. This method takes advantage of the vast number of commercially available heterocycle containing aldehydes and aliphatic or aromatic amines. Methods such as structural and electronic diversity makes this approach well suited to the production of large arrays of compounds for potential application in medicinal or coordination chemistry. Following our strategy, we prepare twenty compounds 37-56 (Figure 3) using the new technology parallel synthesis with robot synthesis with robot (Touzani et al., 2003).

Modulation of pyrazolic tridentate compounds having NCC Junction

The changing of the junction between the two pyrazole moieties and the amines from NCN to NCC was also investigated by the condensation of the known 3-chloromethyl-1,5-diméthylpyrazole 57 with different amines using carbonate as base yielded after three hours reflux in acetonitrile. Six compounds 58-63 were isolated in good Herrag et al., 2006; Bouabdallah et al., 2006b) (Figure 4).



64: $R^1 = CH_3$
65: $R^1 = Pr$
66: $R^1 = {}^tBu$
67: $R^1 =$ neo-Pen
68: $R^1 = Ph$
69: $R^1 = PhCl$
70: $R^1 = CH(CH_3)_2$

71: $R^1 = CH_3$
72: $R^1 = Pr$
73: $R^1 = {}^tBu$
74: $R^1 =$ neo-Pen
75: $R^1 = Ph$
76: $R^1 = PhCl$
77: $R^1 = CH(CH_3)_2$

78: $R^1 = CH(CH_3)_2$; $R^2 = p\text{-}NO_2C_6H_4$
79: $R^1 = CH(CH_3)_2$; $R^2 = o\text{-}NO_2C_6H_4$
80: $R^1 = Pr$; $R^2 = p\text{-}NO_2C_6H_4$
81: $R^1 = Pr$; $R^2 = o\text{-}NO_2C_6H_4$
82: $R^1 = Ph$; $R^2 = p\text{-}NO_2C_6H_4$
83: $R^1 = Ph$; $R^2 = o\text{-}NO_2C_6H_4$
84: $R^1 = CH_2C(CH_3)_3$; $R^2 = p\text{-}NO_2C_6H_4$
85: $R^1 = CH_2C(CH_3)_3$; $R^2 = o\text{-}NO_2C_6H_4$

Figure 5. General pathway for the preparation of library of bipyrazolic compounds.

Synthesis of bidentate ligands based on two pyrazole moieties

We have synthesised new symmetric 5,5'-disubstitued-3,3'-bipyrazole ligands by varying the nature of substituents. It was carried out in ethanol in two steps: the first step aims to elaborate new tetraone compounds 64-70 (Touzani et al., 2001b; Waring et al., 2002). In the second step we condensate the precursor with two equivalents of the hydrazine producing compounds 71-77 in good yields. Compounds 71-77 were selectively alkylated using DMSO/tBuOK to produce 78-85 in good yields (Bouabdallah et al., 2004; Bouabdallah et al., 2006c, 2006d) (Figure 5).

Synthesis of macrocyclic ligands based on pyrazole moiety

Supramolecular chemistry bases its progress in the design of highly organized molecular receptors able to discriminate and/ or induce characteristic properties in given substrates (Lehn, 1995). Among the wealth of molecules that can be the target of recognition are the neurotransmitter catecholamines and are particularly interesting due to their many biological implications. Concretely, dopamine is involved in the normal emotional and autonomic control of humans. The physiological level of dopamine is altered in neurodegenerative and mental illnesses as well as in toxic syndromes induced by cocaine and psychotropic drugs (Campeau et al., 1991). Therefore receptors able to modulate the dopamine level by selective complexation or transport mechanisms represent a research goal of great interest. In this respect, we describe the synthesis of new macrocyclic ligands containing pyrazol and manic coordination sites with good yields. These macrocycles bearing different arms, such as alkyl, phenyl, pyridyl and piperazinic skeleton have two different sizes 88-99 (Berhili et al., 2003; Benabdellah et al., 2007; Touzani et al., 2005; El Kadiri et al., 2008) (Figure 6).

APPLICATIONS

The synthesis of these libraries of compounds with pyrazolic heterocycle units open many doors for potential application, we summarize some examples such as inhibition of the corrosion of steel and copper in acidic media (Benabdellah et al., 2007; El Ouafi et al., 2002; Dafali et al., 2002), which are useful also in the oxidation reaction for miming bio-organic enzymes function (El Kodadi et al., 2008; Boussalah et al., 2009; Bouabdallah et al., 2007a, 2007b, 2007c). We used some of these substrates in the liquid-liquid extraction of toxic metals (Bouabdallah et al., 2006a). Biological application took also place using these compounds as anticancer drugs (El Kodadi et al., 2007). The last application is the theoretical investigations using computational methodologies (Attayibat et al., 2009; Bouabdallah et al., 2006e, 2006f).

Conclusion

The following results can be drawn from this study: (i) Pyrazolic compounds derivatives such as monodentate, bidentate, tridentate and macrocycle can easily be prepared; (ii) All the molecules perform well many potential applications such as corrosion inhibition, catalysis, liquid-liquid extraction, biological and computational calculations; (iii) These interesting results can be applied to other

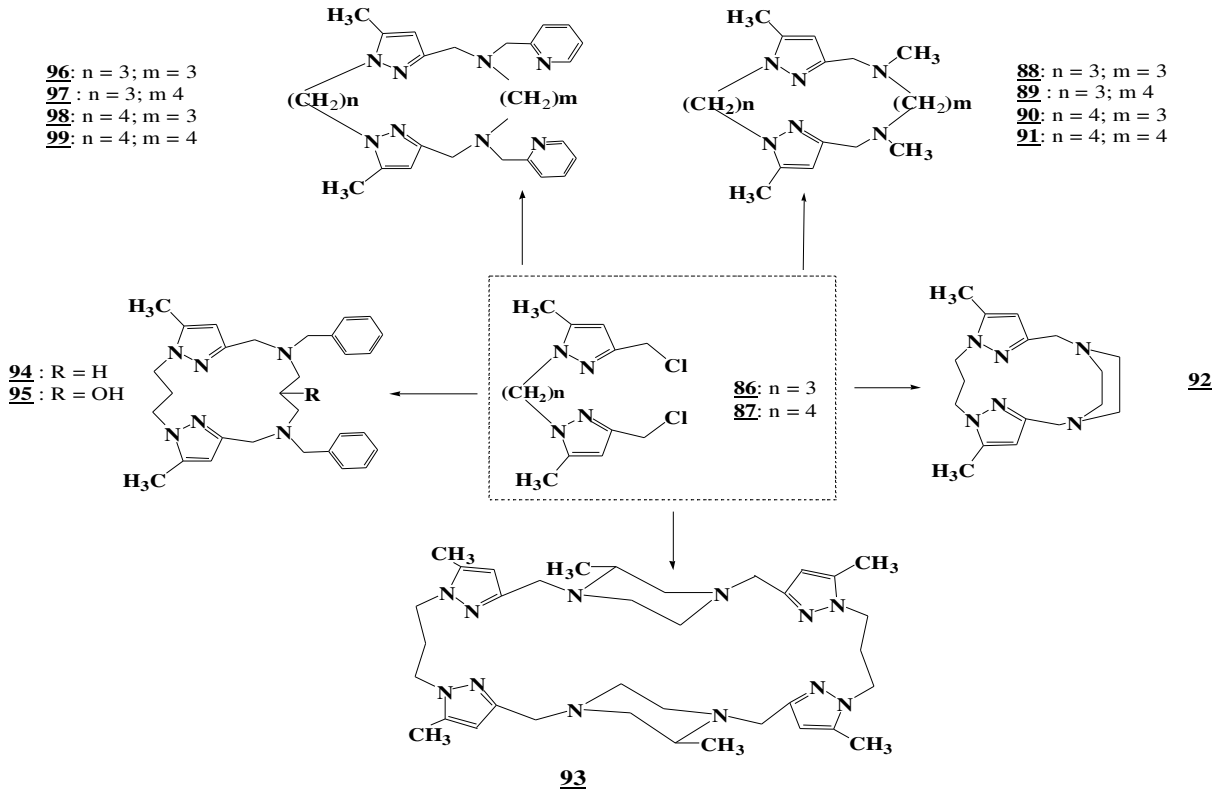


Figure 6. Divers macrocycle compounds with different structural form and cavities.

heterocyclic compounds such as triazole and thiophene…etc.

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