Xanthine-based N-heterocyclic carbenes with nickel: Synthesis and applications

Giulia Francescato, Ana Petronilho
NOVA ITQB, Avd República, 2780-157, Oeiras, Portugal. email: giulia@itqb.unl.pt

INSTITUTO DE TECNOLOGIA QUÍMICA E BIOLÓGICA ANTÓNIO XAVIER | WWW.ITQB.UNL.PT

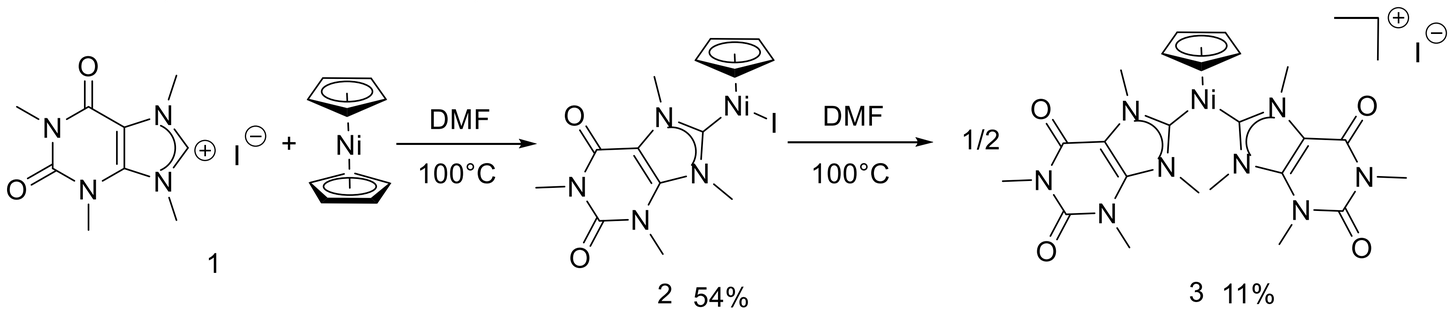
Introduction

In the last decades, fugal infections have become a challenging issue due to substantial increase of fungal resistance to currently available drugs, increasing the incidence of invasive fungal diseases (IFD). The need to find new antifungal agents active against resistant strains is thus mandatory. Candida strains are the most common causes of IFD and among these, infections caused by C. Glabrata, which is resistant to many antifungal agents, are very common. The development of new antifungal agents able to circumvent resistance is thus crucial. Xanthine derivatives are excellent candidates for this purpose and due to their structure, that contains an imidazole ring, their derived salts are excellent ligand precursors for the formation of N-heterocyclic carbenes (NHCs) complexes. In this communication, we report the synthesis of Xanthine-based NHCs stabilized by Nickel, and their corresponding antifungal activity in Candida strains.

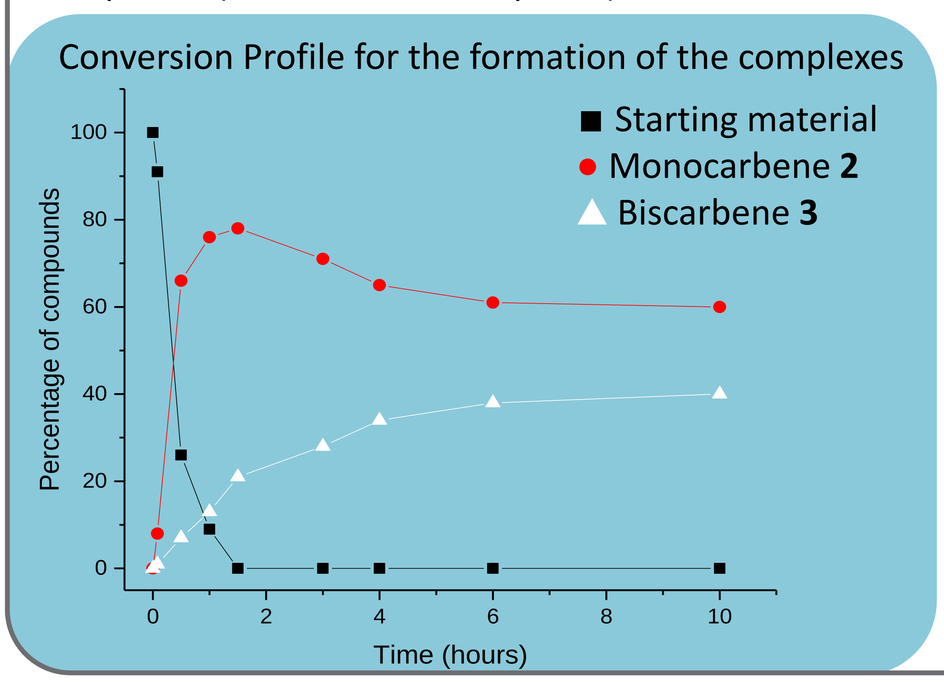
Methyl Caffeine

Two Nickel NHCs (a monocarbene and a biscarbene) have been synthetized starting from methyl caffeine iodide salt as ligand precursor (Scheme I). Complete conversion of the starting material was determined by the disappearance of C8 for both compounds in ^{1}H NMR. The formation of mixtures of both compounds was observed in all cases but appropriate workup allows for their separation.

The reaction was performed in DMF at 100°C and the kinetic of the reaction was examined by ^{1}H NMR. We were able to detect the formation of the two nickel compounds and determine that the major compound (a monocarbene, complex **2**) is formed initially and is an intermediary for the formation of the second compound (a biscarbene, complex **3**).



Scheme I - Synthesis of the nickel complexes **2** and **3**



Crystals of monocarbene suitable for single crystal X-ray diffraction were grown by slow evaporation from a DCM:Et2O solution (Fig 1).

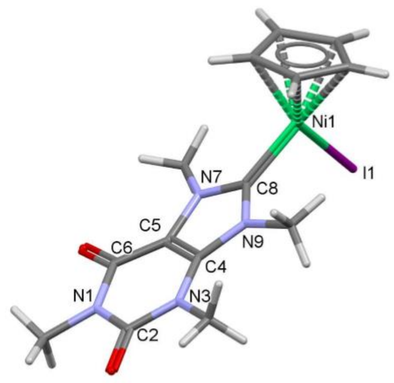
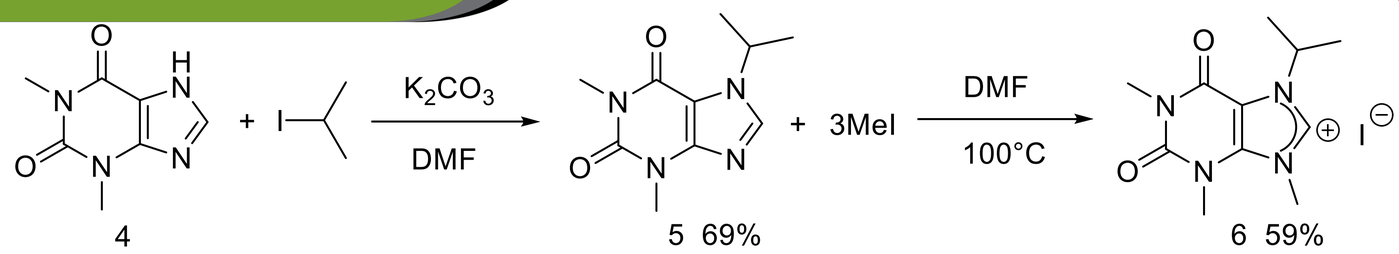


Figure 1

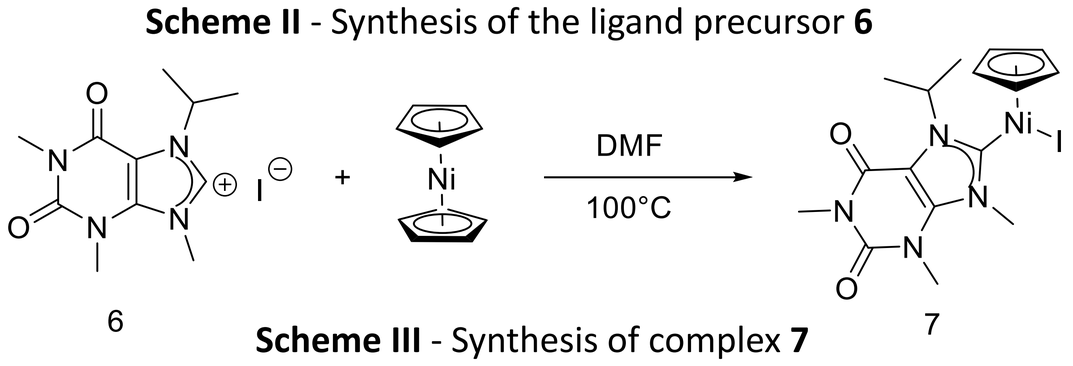
Isopropyl theophilline

The ligand precursor was prepared starting from theophylline which was derivatised with an isopropyl moiety and then methylated to give the iodine salt **6** as shown in scheme II.



Scheme II - Synthesis of the ligand precursor **6**

Compound **6** was then reacted with nickelocene in DMF at 100°C (Scheme III), yielded the monocarbene complex **7** and a degradation product (compound **5**). We monitored the reaction by ^{1}H NMR, concluding that, by contrast with caffeine, the biscarbene compound is not formed. Assuming that the degradation process was a consequence of the high temperature we performed the reaction at a lower temperature (60°C). In doing so we avoided the formation of a by-product and increased the yield from 19% to 39%.



Scheme III - Synthesis of complex **7**

Conclusions

A methodology of synthesis to access Nickel NHC complexes based on Xanthines was developed. Depending on the derivatization at N7 the composition of the final mixture change. Preliminary studies on the antifungal activity tested on two Candida strains (*Candida Albicans* and *Candida Glabrata*) show that complex **2** is a promising antifungal agent for *Candida* strains. Antifungal activity of complex **7** is still under study.

Fungi species	Monocarbene 2 MIC (mM)	Biscarbene 3 MIC (mM)
C. Albicans	0,0625-0,125	none
C. Glabrata	0,03125-0,0625	0,25-0,75

Acknowledgement

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