

Synthesis and scale-up of a pinene pyrimidine type ligand

Authors: Caitlin Blum, *A. Solea & O. Mamula Steiner

Abstract

The aim of this Bachelor thesis was to synthesise a ligand of the pinene-pyrimidine type. Following the literature procedure, α -pinene (racemate) was chosen as starting material and four synthetic steps out of five have been optimised (see Fig. 2) In the first step the formation in situ of the reactant, NOCl, has been tested but the product, the nitrosochloro-derivate, was obtained with a lower yield (20%) compared to the procedure in which exogenous NOCl is bubbled through the reaction mixture (36%). Optimisation of the step 2 (formation of the pinocarvone oxime) was then performed in which various amines and bases were tested, and the highest yield obtained was 39%. The formation of the isoxazole (step 3) worked well and only the purification by distillation caused a decrease of yield to 48% because of the presence of iodine impurities and the small quantity of product to distil. Step 4 (formation of the enamine aldehyde by hydrogenation) was straightforward (yield 99%).

Introduction

The stereoselective synthesis of coordination compounds is an interesting field which received much attention in the last decades. Some pyridine and bipyridine ligands which were rendered chiral with a natural product such as pinene have already been studied. The chirality of the metal centre in the complexes constructed with these ligands can be predetermined.^[1]

This Bachelor thesis was a part of

an on-going project about the synthesis of a new type of pinene-pyrimidine ligand L (Figure 1, left). This type of ligand offers two bidentate sites rather than just one for the pyridine ligands. The introduction of other coordination sites (i.e. carboxylate group) would allow then the formation of heteronuclear metallic complexes. A transition f metal, such as Eu(III), can bind specifically to the oxygen containing site while a d transition metal, such as Ir(III), can bind to the other site (Figure 1, right). An

in a separate flask by the reaction between the NaNO₂ and HCl followed by the bubbling of the resulting NOCl in the reaction flask. This method giving a yield of about 35% is reproducible but is dangerous as well. Since the harmful NOCl gas has to be transferred from a flask to the other, there is a higher risk to come in contact with it. To decrease this risk, we attempted to apply an in situ reaction. In this case, the NOCl gas is directly formed in the reaction flask. A screening of the reaction

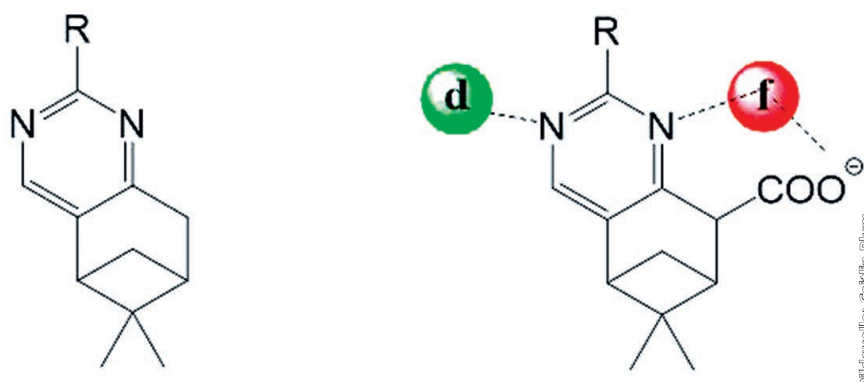


Figure 1: Schematic representation of the Ligand L (left) and its corresponding polymetallic complex (right)

energy transfer could occur between the metals leading to interesting emitting materials^[2]. The synthetic route includes five steps as reported in the literature but previous work in our laboratory has shown that the synthetic steps have to be optimised. For the optimisations, low cost racemate α -pinene has been used as starting material.

Results and discussion

Two procedures were tested for the synthesis of the nitrosochloro-derivate. Firstly, in a method already performed by others in our lab^[3], the NOCl gas was obtained

conditions was performed but the highest yield obtained was about 20% and issues at the reproducibility level were observed.

To increase the low yield reported in literature (about 15%)^[4] for the synthesis of the pinocarvone oxime **P1**, a screening of the reagents (amines and/or bases) and reaction conditions was done. The best result was obtained with pyridine: 39% yield. The purification step still needs to be improved, having the potential to increase the observed yield.

The synthesis of the isoxazole **P2**^[5] proceeds smoothly but the purification by distillation gives better

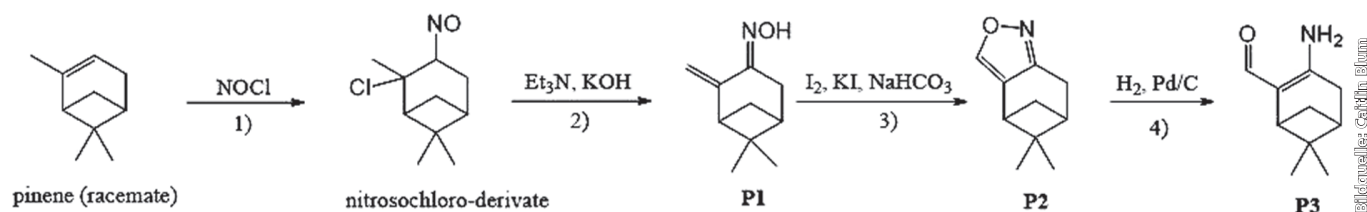


Figure 2: The synthetic scheme for the four successive, optimised steps

results if prior to the distillation, the crude material is washed with an aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ to remove the remaining iodine. After this new washing step followed by the distillation a yield of 48% was reached.

The hydrogenation of **P2** to obtain the enamine aldehyde **P3** worked as described in the literature [6]. The yield was almost quantitative (99%). However, this is the case only if the starting material (**P2**) does not contain any traces of iodine. The Pd/C catalyst is poisoned by the iodine and the yield decreases dramatically.

Conclusion and perspectives

The precursor **P3** of the ligand **L** has been prepared at multi-gram

scale. All the four steps involved were optimised. Initial attempts at mg scale to perform the fifth step leading to the final ligand **L** have been unsuccessful. Further investigations have to be performed for this last step.

References

- [1] T. Bark, M. Düggeli, H. Stoeckli-Evans, A. von Zelewsky, *Angew. Chem. Int. Ed.* **2001**, 40, 2848–2851; A. von Zelewsky, Dr. Olimpia Mamula Steiner, *J. Chem. Soc., Dalton Trans.* **2000**, 219–231.
- [2] P. Coppo, M. Duati, V. N. Kozhevnikov, J. W. Hofstraat, L. De Cola, *Angew. Chem. Int. Ed.* **2005**, 44, 1806–1810.
- [3] A. Solea, A. Hirschi, unpublished results, HEIA, Fribourg, **2018**.
- [4] Yu. G. Pushkin, V. P. Tashchi, A. F.

Rukasov, Yu. A. Baskakov, V. V. Negrebetskii, L. Ya. Bogel'fer, *Zh. Vses. Khim. O-va. im. D. I. Mendeleeva* **1979**, 24, 652 (in Russian).

[5] A. M. Chibiryayev, S. A. Popov, A. V. Tkachev, *Mendeleev Commun.* **1996**, 6, 18–20.

[6] S. A. Popov, A. V. Tkachev, *Heterocyclic Commun.* **2000**; 6, 327–332.



Caitlin Blum, 09.04.1996 from Villarsel-le-Gibloux FR

I started my carrier with an apprenticeship as a Chemistry Lab Technician with integrated maturity at the University of Fribourg in 2015. During the last year of my apprenticeship, I had the opportunity to participate in the Swiss Skills Competition in Bern and won first place. I then decided to continue my formation in chemistry with a bilingual Bachelor at the School of Engineering and Architecture in Fribourg. Following the Swiss Compe-

tition, I was invited, during my first year at school, to participate in the European Competition in Basel and also won first place. My studies as well as the experience of living these competitions allowed me to widen my knowledge and use it for different projects such as my Bachelor thesis in organic chemistry done under the supervision of Prof. Dr. Olimpia Mamula Steiner and A. Solea. I am now going forward with my studies with a Master of Science HES-SO in Life Sciences, major in Chemical Development and Production.