Graphical Abstract

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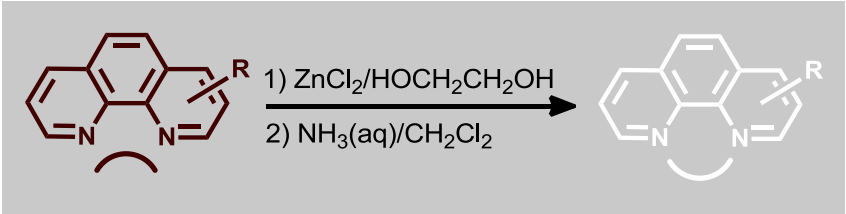

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An effective non-chromatographic method for the purification of phenanthrolines and related ligands

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ABSTRACT

1,10-Phenanthrolines are widely employed as ligands, but their use on a large scale is inhibited by their difficult purification, which usually requires lengthy chromatographic separations. We here describe a purification strategy that takes advantage of the high stability and low solubility of phenanthroline complexes to separate them from the byproducts of their synthesis. Formation of $ZnCl_2$ complexes was employed to this aim, from which the free ligand can be recovered by reaction with aqueous NH_3 in a biphasic CH_2Cl_2/H_2O system. The same strategy was also successfully employed to purify related quinolino-guanidine ligands, showing that the procedure is of more general applicability.

1. Introduction

Phenanthrolines have long been among the most useful and investigated nitrogen ligands, with applications spanning from material chemistry to homogeneous catalysis [1-7]. However, few substituted phenanthrolines are commercially available. We have been involved in their use as ligand for many years [8-13] and we needed to synthesize some substituted phenanthrolines that are either not commercially available or not even previously reported in the literature [14-19]. As for other researchers working with phenanthroline ligands [20-30], our aim is to develop catalytic reactions that may be employed at an industrial scale, we were interested in synthetic strategies that only require cheap reagents. Many different synthetic pathways exist for the preparation of phenanthrolines, but when cost and availability of reagents are a concern, Skraup type condensation reactions are invariably employed. These reactions always produce many byproducts that still contain basic nitrogen atoms and cannot be eliminated by a simple acidic extraction/back extraction. A simple crystallization is most of the time insufficient to obtain an analytically pure compound. On the other hand, chromatographic purification of phenanthrolines is notoriously difficult and strongly limits the scale of the preparation.

Based on our previous experience with Ar-BIAN (Ar-BIAN = *bis*-aryliminoacenaphthene) type of ligands [31-34], we considered that the formation of a (phenanthroline)$ZnCl_2$ complex may be a step of an effective purification strategy because such complexes are very insoluble, whereas $ZnCl_2$ complexes of monodentate nitrogen ligands are much more soluble. In the case of Ar-BIAN and even Alk-BIAN ligands, [35-37] the procedure we developed to remove the coordinated zinc, that is treating a CH_2Cl_2 solution or suspension of the $ZnCl_2$/ligand complex with an aqueous solution of potassium oxalate, is very efficient and has become the standard procedure employed in the literature to effect this decomplexation. The ligand remains in the organic phase, whereas zinc either form insoluble ZnC_2O_4, or remains in the aqueous phase as a mixture of $[Zn(C_2O_4)_2]^{2-}$ and $[Zn(C_2O_4)_3]^{4-}$ depending on oxalate concentration. We thus decided to test if a complexation/decomplexation procedure may be effective in purifying phenanthrolines without having to resort to column chromatography.

2. Results and discussion

In order to synthesize the skeleton of phenanthroline molecules, in our laboratories we commonly employ the procedure described by Bernhard [38] and co-workers. This involves the reaction of an α-β unsaturated aldehyde with a suitably substituted 8-aminoquinoline in 70% H_2SO_4, employing sodium iodide as a catalyst. This procedure is in turn adapted from one previously reported for the synthesis of quinolines [39, 40] and has the advantage of avoiding highly toxic arsenic compounds as in the classical procedure. In our hands, the procedure reliably worked in many cases, but the crude compound is always dark brown and a chromatographic purification is needed to obtain a colorless compound, as also reported in the original paper. As an alternative, we also employed in one case *m*-nitrobenzenesulfonic acid as the

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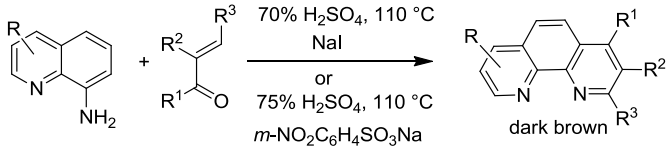
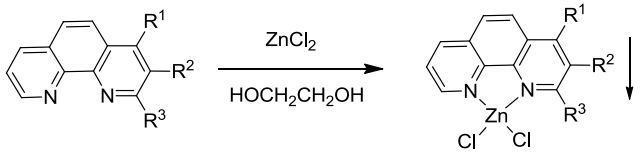
oxidant.[15, 41] This is also an effective reagent, but its use does not solve the problem of the insufficient purity of the product obtained by a simple acidic extraction/back-extraction procedure (Scheme 1).



Scheme 1. General synthetic strategy employed for the synthesis of phenanthrolines.

In this work, we employed the synthesis of 4-methyl-1,10-phenanthroline (4-MePhen, R^1 = Me, R^2= R^3 = R = H in Scheme 1) to optimize our purification strategy. The ^{1}H NMR spectrum of the product obtained by employing NaI as reagent, after the standard acidic extraction/back extraction procedure, is shown in Figure 1a. Apart from the main peaks, due to the desired product, many smaller intensity peaks are clearly visible.

The first aspect that needed attention is the choice of the solvent for the complexation step. It should be polar enough to dissolve $ZnCl_2$, but should also not coordinate strongly to zinc or dissolve the final complex. It should also dissolve well all organic impurities. Ethylene glycol was found to give best results, with acetic acid also being employable (methanol and other alcohols do not dissolve $ZnCl_2$ efficiently even when hot, Scheme 2).

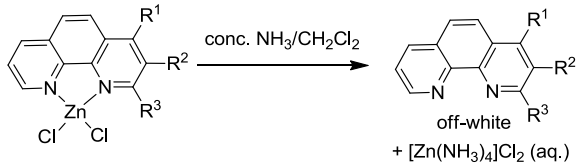


Scheme 2. Formation of the zinc complex.

We performed the complexation step under different conditions in order to maximize the yield of the complex, still leaving most impurities in solution. The best strategy consisted in mixing two ethylene glycol solutions of the phenanthroline and of $ZnCl_2$ at around 50 °C and then heating at 100 °C to complete the coordination step, followed by slow cooling. The solid complex was separated by filtration on a Buchner funnel at room temperature and subjected to a further purification step by heating it in fresh ethylene glycol. This step cannot be considered a true recrystallization because the complex is only little soluble even in the hot solvent, but still succeed in removing some additional impurities, as inferred from the color of the solvent after the procedure.

To remove the $ZnCl_2$ moiety from the phenanthroline ligand, we initially tested the same conditions employed by us for the analogous step in the synthesis of Ar-BIAN and Alk-BIAN ligands. However, when the same protocol was applied to the present case, an even less soluble precipitate and no free ligand was obtained. The identity of the precipitate was not investigated in detail, although formation of [Zn(Phen)(C_2O_4)] is a reasonable possibility. In any case, oxalate is clearly not suitable to remove zinc in this case.

Complete decomplexation of zinc from the phenanthroline could on the other hand be obtained by substituting the oxalate solution with a concentrated aqueous ammonia solution, where zinc cations are present in the form of $[Zn(NH_3)_4]^{2+}$ [42].



Scheme 3. Decomplexation procedure.

The ^{1}H NMR of the so obtained product is shown in Figure 1b. It is immediately evident that none of the previously observable extra signals is any longer present. The compound is also analytically pure, but is not completely colorless. The solid is off-white, but its solutions still show a tan color that may constitute a problem if the optical or optoelectronic properties of its complexes must be investigated. For any synthetic use, however, the purity of the compound is clearly sufficient.[43]

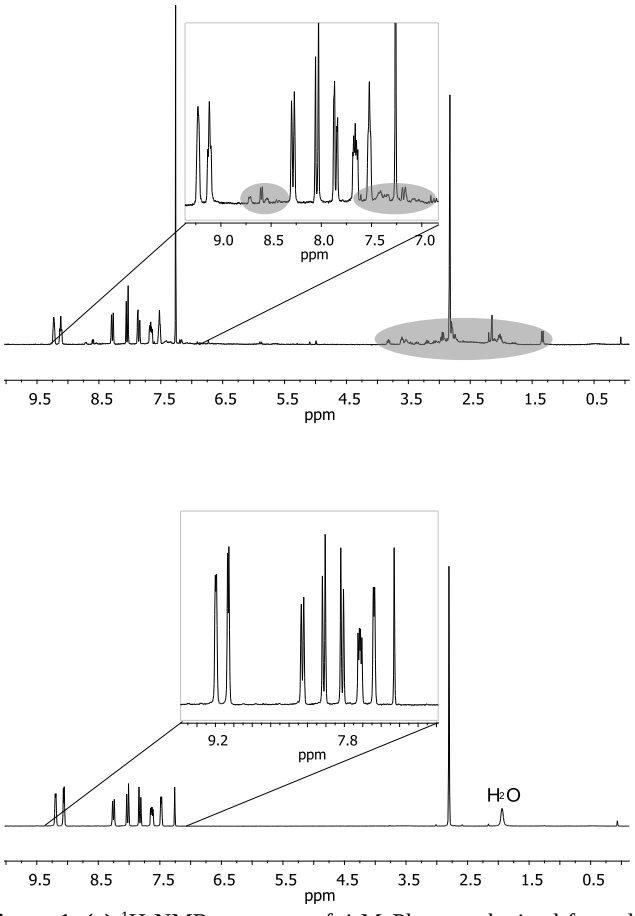


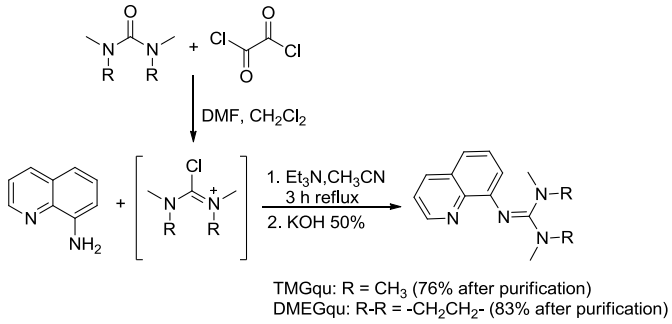
Figure 1. (a) ^{1}H NMR spectrum of 4-MePhen as obtained from the reaction employing NaI, after acidic workup. **(b)** Same after the purification procedure described in this paper.

The global yield of the synthesis+purification was only 60%. In order to test if the fair yield of the purified compound is due to a lack of selectivity in the synthesis or to losses in the purification, the efficiency of each step of our protocol was tested on pure 1,10-phenanthroline, where the yield may possibly be 100%. The complex [$ZnCl_2$(Phen)] was obtained in a 98% yield following the same procedure employed for 4-MePhen. The "recrystallization" step allowed to recover 95% of the complex, whereas the decomplexation step proceeded in essentially quantitative yield. Thus, the overall efficiency of the procedure was 93%, with the recrystallization step being the weaker point of the protocol.

The synthesis of 4-MePhen was also performed employing *m*-nitrobenzenesulfonic acid as co-oxidant. The corresponding spectra are reported in the Supplementary Material. Again, many impurities were present in the product after the acidic work-up, which could be eliminated by the $ZnCl_2/NH_3$ treatment. The global yield was very close to that obtained with the previously described method (61 %), but the product was of a lighter color since the beginning and was almost colorless after the purification strategy. Although this is an advantage, it should be noted that *m*-nitrobenzenesulfonic acid and the products derived from its reactions have a strong tendency to generate foams during the extraction/back-extraction steps, making the separation more difficult.[44]

The same protocol was then applied to the synthesis of 3,4-dimethylphenanthroline (3,4-Me_2Phen) with good results (52 % overall yield of the purified material).

To test if the protocol may be useful even in the case of other chelating ligands, it was employed for the purification of two quinoline-guanidine hybrid ligands. These ligands have been previously reported. In the original article, they were apparently obtained in a pure form without any chromatographic workup.[45] Although this may be due to a high purity of the reagents, when we performed the same synthesis (Scheme 4) with the commercially available 8-aminoquinoline, a greenish product was obtained that needed a chromatographic purification to give the pure yellow compound.[15] The only variation in our procedure is that the intermediate chloroformamidiunium salt was prepared by the reaction of 1,3-dimethyl-2-imidazolidinone or tetramethylurea with oxalyl chloride [46], instead of employing the highly toxic phosgene as reported in the previously published account.



Scheme 4. Synthesis of quinoline-guanidine ligands.

The purification protocol here described worked well even for these ligands, indicating that it is not limited to phenanthrolines and may be of more general use. Note that TMGqu is an oil when non-coordinated. Thus it could not be purified by crystallization, whereas its $ZnCl_2$ complex is a crystalline solid.

3. Conclusions

We have described a purification protocol for phenanthrolines and related chelating ligands that takes advantage of the low solubility of their complexes with respect to that of non-chelating or weakly chelating byproducts, such as those that are always formed during the reaction and would not be separated by an acidic work-up. The procedure can be applied to multi-gram preparations only requiring cheap and non-toxic reagents and limited amounts of solvents. The method also worked for quinoline-guanidine hybrid ligands, showing that it can be of more general applicability. There are obviously also limitations. The method is not applicable to phenanthrolines having hydrolytically sensitive groups (we could not apply it to 4-methoxyphenanthroline) and is probably of lesser use when the synthesis of the phenanthroline involves the functionalization of a pre-existing phenanthroline rather than the creation of a new heteroaromatic ring. However, most complex ligands are usually prepared by multistep procedures requiring the intermediate formation of simpler derivatives and the protocol here described could still be useful at this stage.

Acknowledgments

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[42] Use of ammonia is not suggested for standard Schiff bases, since basic conditions may cause the hydrolysis of the ligand.
[43] Use of decolorizing carbon or reduction by an hydridic reagent (best NaH in our hands) allowed obtaining an even clearer compoundt at the expense of some product loss, but we did not optimize these strategies.
[44] Some unreacted 8-aminoquinoline was present among the "impurities" when *m*-nitrobenzenesulphonic acid was employed. It was not the purpose of this work to optimize the reagents amounts for this synthesis and the same ratios and reaction time employed for the NaI-based procedure were used. However, it is clear that margins for improvement exist.
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Supplementary Material

Experimental procedures and copies of NMR spectra.