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ARTICLE TYPE

A new route to dithia- and thiaoxacyclooctynes via Nicholas reaction

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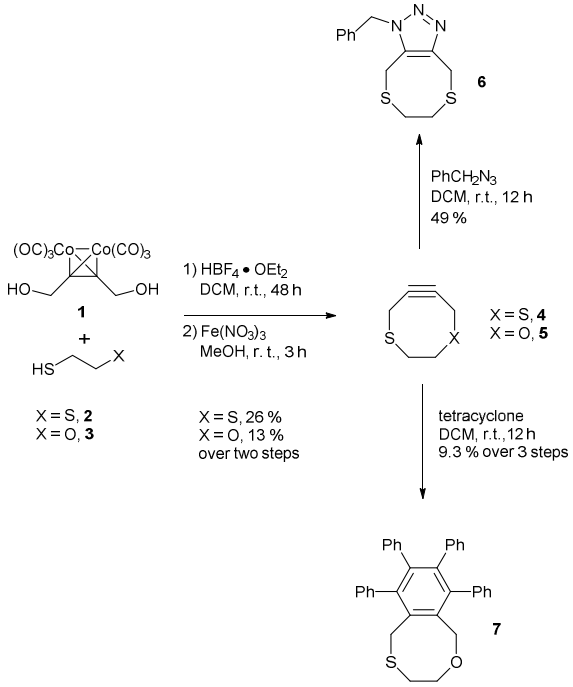
The current paper describes a new synthesis of heteroatom-substituted cyclooctynes. By using the Nicholas reaction we managed to design a concise synthesis that only uses three steps to build the eight-membered ring. It was also possible to functionalize said alkyne with a fluorophore.

Cyclooctynes have developed into an important class of compounds that are used as highly versatile tools in chemical biology. [1-13] They are applied as chemical reporters in strain-promoted click reactions to label various kinds of biomolecules like glycans,[14] proteins[15] and DNA[16, 17] as well as in material sciences.[18] Their synthesis usually comprises many steps, the final one being the generation of the triple bond. Widespread reactions that are used to obtain the alkyne moiety are elimination reactions starting from vinyl bromides,[19] ketones,[20] enol triflates[2] and related elimination reaction precursors. Furthermore there are other possibilities like the oxidation of dihydrazones,[21] thermal decomposition of selenadiazols[22] or the irradiation of cyclopropenones.[23] The incorporation of an intact alkyne group through a ring closing reaction is hardly ever used because the ring strain building up during the course of reaction usually prevents the ring formation. There are examples, however, where heteroatom-substituted cyclooctynes were synthesized by S_N2 ring formation between 1,2-ethanedithiol and 1,4-dibromo-2-butyne as shown by *Meier et al.*.[24] This type of reaction, though possible, results in considerable by-product formation. Several reactions were reported which use the Nicholas reaction to build up similar (macro-)cyclic compounds.[25-27] The Nicholas reaction is a reaction starting from a dicobalt hexacarbonyl-alkyne complex bearing an oxygen atom in the propargylic position.[28-30] By adding an acid it is very easy to generate a carbocation in the propargylic position that can then in turn react with a suitable nucleophile. To our knowledge the scope of the double Nicholas reaction to generate (hetero)cyclooctynes in one step has not been fully explored.[31-41] However, as mentioned above, there have been syntheses of cyclooctyne dicobalt complexes that were used directly in various transformations, i. e. Pauson-Khand reactions, without generating the decomplexed alkyne.[42-44]

The route started with the synthesis of the cobalt complexes of 1,4-dithia-6-cyclooctyne and 1-thia-4-oxa-6-cyclooctyne using the starting material 1,4-but-2-ynediol as described by *Went et al.*[27]. Therefore starting complex **1**[45] was dissolved in dichloromethane, the nucleophile (**2** or **3** respectively) and finally HBF_4-etherate as the acid catalyst were added and the mixture was stirred at r.t. for 48 h. The resulting complexes were then treated directly with ferric nitrate in methanol and leading to the cyclooctynes **4** and **5** as oils exhibiting a typical odor. Alkynes **4** and **5** were obtained in 26% and 13% yield respectively (Scheme 1). Comparable yields were obtained for the formation of a less strained cyclononyne by Young *et al.* [36]



Scheme 1: Synthesis of heterocyclooctynes and further conversion.

The dithiacyclooctyne **4** was then treated with benzyl azide to accomplish a strain promoted click-reaction. In our attempts to react the thia-oxa cyclooctyne we chose tetracyclone as a reactant to avoid the formation of regioisomers. In both cases the reactions worked out, yielding the expected products. We then tried to vary the scope of the reaction by changing the nucleophile to a glycol derivative, bearing only oxygen atoms and no sulphur. Glycol itself proved to be an unsuitable reaction partner in the Nicholas reaction, as did pinacol, glycerol and methyl glycerate. It was possible, however, to observe a reaction with *meso*-1,2-dimethylglycol, affording the corresponding dicobalt hexacarbonyl complex (**8**). However, the deprotection to the free alkyne did not yield the anticipated cyclooctyne.

Besides the aliphatic dithiols, there are also aromatic dithiols that

were used in literature procedures[46, 47] to build up macrocyclic dicobalt-alkyne complexes. We therefore also investigated the use of 1,2-benzenedithiols, *o*-mercaptophenol, 2-aminothiophenol and 3,4-dihydroxy methyl benzoate. We observed no product formation for the reaction of the aromatic diols. And also *o*-mercaptophenol could not be reacted successfully to the desired product. We were not able to identify the side products, that were formed but we assume that the generated cations react in an electrophilic aromatic substitution. However, it was possible to isolate the products of the reaction between the dicobalt hexacarbonyl complex of 1,4-but-2-ynediol (**1**) and 1,2-benzenedithiol or 2-aminothiophenol,the complexes **10** and **9**, respectively, both in acceptable yields (51% and 31%).

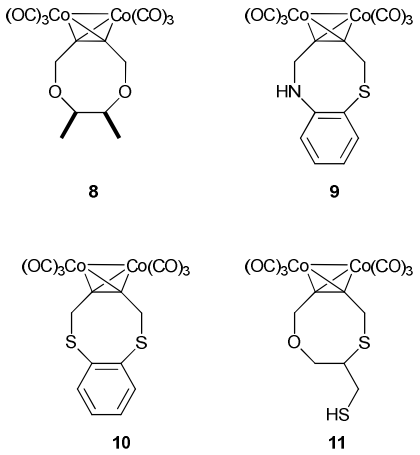
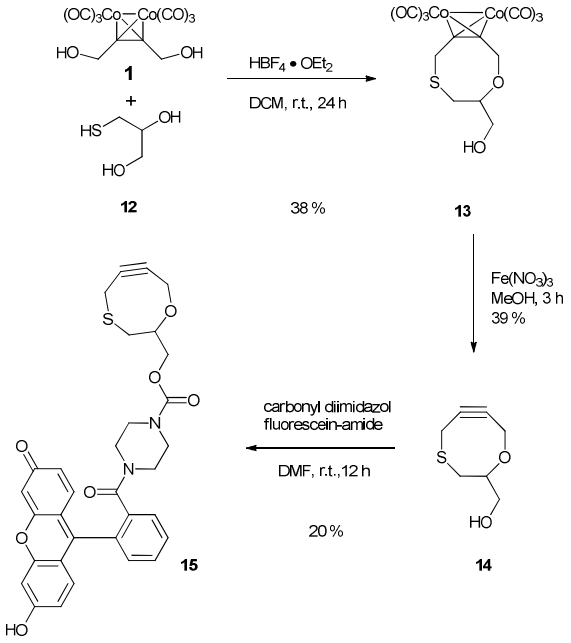


Figure 1: Synthesized complexes, without deprotection.

Some of the complexes are not suitable for mild deprotection. The standard procedure for the oxidation of the complexes to the free alkyne used 5.00 equivalents of ferric nitrate in a methanolic solution at room temperature. Under the conditions the free cyclooctyne could not be observed in cases of complex **9** and **10**. Also the variation of reaction conditions (e. g. lower temperature and different amounts of the oxidizing agent) did not yield the desired metal-free cyclooctynes. We then tried to use the known cyclooctyne scavenger tetracyclone to determine whether the alkyne was formed at all during the reaction. Interestingly we were able to detect the masses of both products in the crude product, showing that the deprotection indeed worked. However, even after the detection of the scavenged product in the MS-spectra neither the alkyne nor the alkyne-tetracyclone reaction products could be isolated from the respective reactions' raw products.

After the aromatic nucleophiles, we wanted to explore the possibilities to attach an additional functional group, in order to have a means to functionalize the alkyne. We studied further possible substances and used 2,3-dimercapto-1-propanol and 1-thioglycerol (**12**) to yield cyclooctynes with an additional alcohol group. The reaction with 2,3-dimercapto-1-propanol was investigated first, expecting that the product would be the dithiacyclooctyne-ring due to the higher nucleophilicity of the sulfur. The reaction worked but when we examined the NMR spectra we realized that the wrong isomer was formed. Instead of the desired dithia-product we were able to synthesize the thia-oxa-product (**11**, Figure 1). Due to the fact that the free thiol is prone to oxidation under oxidizing deprotection conditions, it was not suitable for further functionalization. Therefore the alternative 1-thioglycerol (**12**) was used and thus the desired complex **13** could be obtained and be further deprotected to the cyclooctyne **14** (Scheme 2). To further functionalize it, we used carbonyldiimidazole to attach fluorescein-piperazine-amide as a carbamate. Thus we were able to synthesize a new cyclooctyne dye conjugate **15** in only four steps. Such cyclooctyne-dye conjugates are useful tools in cell labelling.



Scheme 2: Synthesis of a new fluorescein-cyclooctyne.

In summary, we were able to devise a new route to heterocyclooctynes *via* Nicholas reaction. Thus we were able to synthesize heteroatom-cyclooctynes in only three steps and a dye-functionalized cyclooctyne in four steps, starting from commercially available 1,4-dihydroxy-but-2-yne. This sequence is one of the shortest syntheses of the cyclooctyne scaffold to date.

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Notes and references

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