Synthesis of Pyridine-Containing Macrocycles by Cobalt-Mediated Trimerization of Triply-Bonded Species

Alessandro F. Moretto, Han-Cheng Zhang, and Bruce E. Maryanoff*

The R.W. Johnson Pharmaceutical Research Institute Spring House, Pennsylvania 19477

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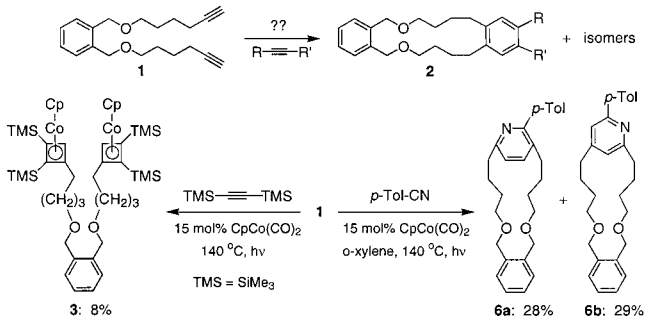
Transition metal reagents have garnered an important role in the synthesis of cyclic organic compounds.[1] Recently, ring-closing metathesis (RCM)[2] has emerged as a powerful method for generating diverse ring systems, including macrocycles,[3] and intramolecular cyclopropanation has also been remarkably successful.[4] These reactions are noteworthy among transition metal-mediated cyclizations because of the efficient formation of medium- and large-size rings, which probably derives from the ability of the metal to coordinate both ends of the acyclic substrate to pre-organize the system and reduce entropic costs. Beyond these reaction classes, there is a paucity of useful transition metal-mediated macrocyclization techniques.[5]

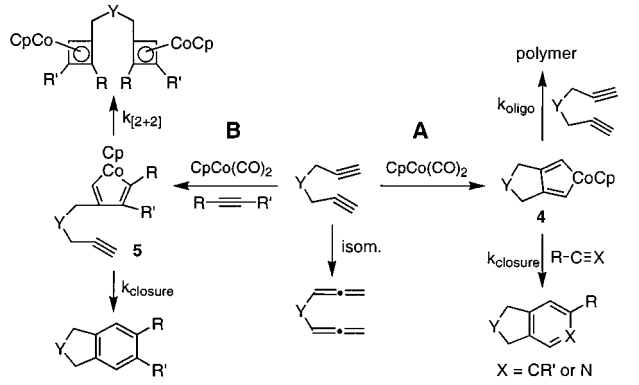
We became interested in the potential of cobalt-catalyzed alkyne cyclotrimerization[1i] as a macrocyclization method. The proposed process is exemplified by the conversion of bis-alkyne **1** to arene-fused macrocycle **2**, along with possible meta- and paracyclophane isomers (Scheme 1). In this transformation, the transition metal could well provide a templating effect by coordination of the alkyne termini of **1** followed by intermolecular cycloaddition of another alkyne. Of course, the key issue is identifying reaction conditions that would favor the desired reaction pathway.

Although there are some reported examples of intramolecular cobalt-mediated alkyne trimerization, the formation of macrocycles has been limited to the synthesis of polycyclic cage compounds, wherein all three alkyne groups are tethered to the same backbone.[6] A previous attempt to execute the more challenging intermolecular reaction was unsuccessful in that the cobalt-mediated addition of a long-chain bis-alkyne to a monoalkyne yielded a stable bis-η^4-cyclobutadienecobalt complex.[7] We have investigated this area of chemistry and now describe the successful macrocyclization of long-chain bis-alkynes with *nitriles* to obtain fused pyridine macrocycles, particularly *pyridine-cyclophanes*. Also, we report the regiospecific macrocyclization of an alkyne-nitrile with an alkyne.

Scheme 1



Scheme 2



Initially, we conducted studies on macrocyclization of a bis-alkyne and a monoalkyne to produce arene-cyclophanes. However, reaction of bis-alkyne **1** with excess bis(trimethylsilyl)acetylene in the presence of $CpCo(CO)_2$ (15 mol %) at 140 °C, with irradiation by visible light, did not yield any desired macrocycle. Rather, a bis-cyclobutadiene−cobalt complex, **3**, was formed in 8% yield (∼100% yield relative to catalyst loading). On reducing the relative concentration of the monoalkyne to 1 equiv (with *o*-xylene as solvent), we obtained only intractable presumably polymeric material. The negative results for this reaction can be appreciated by analysis of the mechanism of cobalt-catalyzed alkyne cyclotrimerization (Scheme 2).[8]

The first step is formation of two possible cobaltacyclopentadiene intermediates, pathways **A** and **B**. If **A** is taken, then intermediate **4** would be formed, and it could coordinate with the alkyne monomer to give the desired ring closure or with the bis-alkyne to give oligomers. It has been shown that this intermediate will not form stable cyclobutadiene−cobalt complexes.[7] If path **B** is taken, then intermediate **5** would be formed, and it could proceed to a stable bis-η^4-cyclobutadiene−cobalt complex (by formal [2 + 2] cycloaddition) or the desired ring-closed product. From our isolation of **3**, it appears that pathway **B** predominates in this case and that the rate of ring closure to the desired product ($k_{closure}$) is much slower than the rate of cyclobutadiene complex formation ($k_{[2+2]}$).

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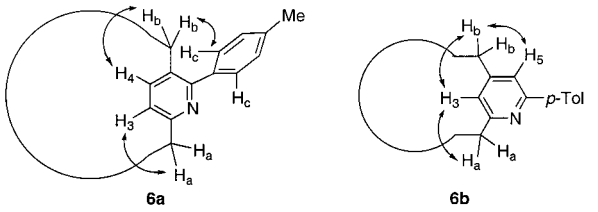


Figure 1. Observed NOEs for **6a** and **6b**.

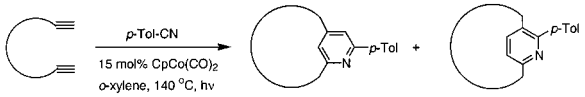
We reasoned that, if the monomeric triply-bonded species were a nitrile instead, then pathway **B** would be inaccessible because Co(I) will not readily coordinate with a nitrile's lone-electron pair. Only *after* metallacycle formation, when the metal exists as Co(III), will the nitrile coordinate and insert.[9] Consequently, only **4** would be generated, and the competing pathways available to it are insertion of the monomeric nitrile to form a fused-pyridine macrocycle ($k_{closure}$) and insertion of a second equivalent of bis-alkyne to form oligomeric products (k_{oligo}). Adjusting the effective concentration of bis-alkyne via syringe pump techniques ought to minimize the undesired side reaction and favor the desired macrocycle, hopefully in synthetically useful yields.

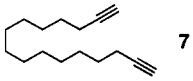
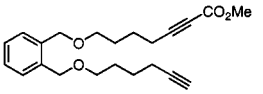
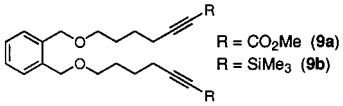
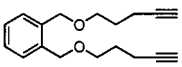
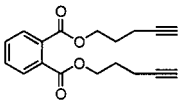
Reaction of bis-alkyne **1** with *p*-tolunitrile provided two pyridine-macrocycles, **6a** and **6b**, in a rather reasonable 57% yield (Scheme 1), along with a trace of the corresponding bis-allene, an isomerization product (Scheme 2).[10] The regioisomeric 2,3,6-trisubstituted and 2,4,6-trisubstituted pyridines (para- and meta-cyclophanes, respectively) were formed in a ratio of 1:1. The identification of **6a** and **6b** was based on ^{1}H NOESY spectra (Figure 1). Notably, the sets of benzylic protons, H_a and H_b, exhibited a strong NOE with the pyridine protons, in a distinct pattern for each isomer.

To probe the factors that control the regioselectivity of this reaction, we subjected various bis-alkynes to the cyclotrimerization process (Table 1). Substrate **7**, which is less conformationally constrained than **1**, also gave a 1:1 mixture of regioisomers, but with a reduced yield of 42%. Capping of the terminus of one alkyne of **1** with an ester group, as in **8**, resulted in a 3:1 ratio of regioisomers in favor of the metacyclophane, although the yield was significantly reduced. This low yield is probably due to increased steric bulk in the substrate, which may inhibit insertion of the nitrile into the metallacycle intermediate, thus allowing a significant amount (27% yield) of the bis-allene side product to be formed. Consistent with this view, bis-capped substrates **9a** and **9b** did not undergo cyclotrimerization under these conditions. When the tether length was shortened by two methylene units, as in **10**, the desired products were obtained in 61% yield with a 1:5 ratio in favor of the paracyclophane. This outcome may reflect a conformationally unfavorable transition state for formation of the metacyclophane, given the reduced ring size relative to that for **1**. Addition of conformational constraint by replacing two methylenes with carbonyl groups, as in **11**, increased the regioselectivity to 1:7 in favor of the paracyclophane.

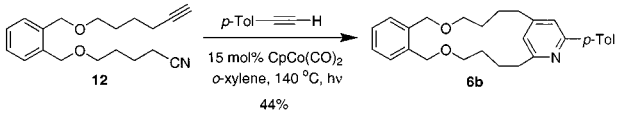
Analogously, in the reaction of **1**, *p*-methoxybenzonitrile gave a 38% combined yield of macrocyclic products, as a 1:1 mixture of regioisomers, while *p*-carbomethoxybenzonitrile gave a 36% combined yield with a 2:1 ratio favoring the metacyclophane. Cyclohexylnitrile and butyronitrile reacted poorly with **1**, providing only trace amounts of macrocyclic products. However, cinnamonitrile gave a 43% yield of adducts with a 2:1 ratio of regioisomers favoring the paracyclophane.

Table 1. Pyridine-Cyclophanes from Bis-Alkynes



bis-alkyne substrate	yield (%)	products, *meta*:*para*
 **7**	42	1:1
 **8**	22	3:1
 R = CO_2Me (**9a**) R = $SiMe_3$ (**9b**)	0	
 **10**	61	1:5
 **11**	34	1:7

Scheme 3



A particularly noteworthy result derives from tethering an alkyne and a nitrile together, as with **12**, and adding a monoalkyne (Scheme 3). Under our standard protocol, *p*-tolylacetylene and **12** exclusively afforded metacyclophane **6b** in 44% yield. An analysis of the three likely intermediate metallacycles and the six corresponding cyclophane products indicates that the observed product is formed regiospecifically from the transition state with the least unfavorable steric interactions and conformational strain.

In conclusion, we have developed a cobalt-based macrocyclization protocol that generates pyridine-cyclophanes from bis-alkynes and nitriles, or alkyne-nitriles and alkynes, in synthetically useful yields. By producing a macrocycle and a small aromatic ring concomitantly, this process furnishes substantial molecular complexity in a single step. In that sense, this chemistry nicely complements the RCM-based and cyclopropanation-based macrocyclizations.[2−4] It is noteworthy that we incorporate an external triply-bonded species in a *bimolecular process*. This brings another diversity element into the product, which should be conducive to the generation of interesting pyridine-cyclophane libraries. We are continuing to study this macrocyclization process to assess its scope and limitations, and to extend it to alkyne trimerization.

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Supporting Information Available: Synthetic details and product characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For a typical experimental procedure, see Supporting Information. Our macrocyclization procedure is virtually the same as that used to form small rings via cobalt-catalyzed alkyne trimerization.