Concise Copper-Catalyzed Synthesis of Tricyclic Biaryl Ether-Linked Aza-Heterocyclic Ring Systems

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ABSTRACT

A new method for the synthesis of tricyclic biaryl ether-linked ring systems incorporating seven-, eight-, and nine-membered ring amines is presented. In the presence of catalytic quantities of copper(I), readily accessible acyclic precursors undergo an intramolecular carbon/oxygen bond-forming reaction facilitated by a “templating” chelating nitrogen atom. The methodology displays a broad substrate scope, is practical, and generates rare and biologically interesting tricyclic heteroaromatic products that are difficult to access by other means.

Tricyclic aza-heterocyclic ring systems incorporating a biaryl ether motif are present in a number of biologically active and pharmaceutically relevant compounds and thus constitute very attractive synthetic targets. For example, the dibenzoazepinones1 and dibenzoazepines2 have been shown to exhibit significant biological activities (Figure 1). The dibenz[b,g][1,5]oxazocines, which contain a tricyclic biaryl ether-linked ring system incorporating an eight-membered ring amine, are comparatively much less well studied, but some are known to be CNS active and are used for the treatment of pain and/or inflammation.3

Despite these interesting biological properties, examples are relatively rare; analogous compounds containing seven- and nine-membered amine ring systems are extremely scarce. Consequently, compounds of this sort (indeed, seven-nine membered cyclic biaryl ethers in general) are underrepresented in current small molecule screening libraries. This can mainly be attributed to synthetic difficulties; for example, there are notable problems associated with medium ring synthesis, with medium ring biaryl scaffolds representing especially challenging targets.4,5 Overall, there are a lack of

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efficient, concise, and flexible strategies toward diversely substituted dibenzo[\(b,g\)][1,5]oxazocines and equivalent biaryl ethers with seven- and nine-membered ring amines. New methodology of broad utility for the synthesis of these scaffolds is needed so that their biological usefulness can be investigated and exploited further.

Recently, we reported the development of a novel copper-catalyzed strategy for the synthesis of medium ring nitrogen-linked biaryl systems \(3a\) (Scheme 1).\(^6\) Our approach was based around the direct \(N\)-arylation of acyclic precursors of the general form \(4a\), which incorporated a “templating” aliphatic nitrogen atom in addition to an aniline nitrogen and aryl bromide. Our mechanistic hypothesis is that both the aniline nitrogen and aliphatic templating nitrogen atom bind to the copper atom, forming a species, \(5a\), in which the copper metal is incorporated in a chelate with the substrate. This ligation is followed by oxidative addition to the aryl halide, forming \(6a\), and subsequent reductive elimination yields the cyclized product. The presence of the templating nitrogen atom was found to be crucial for cyclization.\(^7\) We envisaged that the same mechanistic blueprint could be applied to a carbon–oxygen bond formation manifold, which would enable access to oxygen-linked biaryl oxazacine systems \(3b\) from acyclic precursors \(4b\). The validity of this approach had been established in our previous study; the synthesis of one oxygen-linked medium ring biaryl ether was accomplished by direct cyclization of a phenolic acyclic precursor using a slightly modified version of the optimized reaction conditions employed for the synthesis of nitrogen-linked biaryls.\(^8\) However, the yield of the desired cyclic product was extremely low, which clearly limited the utility of this method.

**Scheme 1. Mechanistic Blueprint for the Copper(I)-Catalyzed \(N\)- and \(O\)-Linked Biaryl Cyclization Process**

![Chemical structure](image)

\(\text{X} = \text{NH}_2, \text{Y} = \text{NH} \quad 4a\)

\(\text{X} = \text{OH} , \quad 4b\)

\(\text{Cu(I)} \rightarrow \text{ligation} \rightarrow \text{oxidative addition} \rightarrow \text{reductive elimination}\)

**Notes:**

\(\text{The “templating” aliphatic nitrogen atom is circled. Possible ancilliary ligands omitted for clarity.}\)

Herein we describe the development of a new, concise, and efficient protocol of broad applicability for the preparation of a range of compounds based around rare and biologically interesting tricyclic biaryl ether-linked scaffolds incorporating seven-, eight-, and nine-membered ring amines.\(^8\) Application of this methodology should allow the sampling of attractive regions of chemical space that are under-exploited in current drug discovery efforts.\(^9\)

Initial optimization studies were directed toward the ring-closure of acyclic precursor \(7\), readily generated by a three-step sequence (Scheme 2). Reductive amination of (2-bromo)benzylamine \(8\) and salicylaldehyde \(9\) led to the formation of amine \(10\). Subsequent treatment of this crude product material with formaldehyde yielded cyclic hemiaminal \(11\), and reduction in acid provided \(7\) in a high overall yield, with chromatography required only at the final stage.\(^10\) This proved to be a general and robust route to a wide variety of cyclization substrates (see the Supporting Information).

\(\text{X} = \text{NH}_2, \text{Y} = \text{NH} \quad 3a\)

\(\text{X} = \text{OH} , \quad 3b\)

\(\text{Cu(I)} \rightarrow \text{ligation} \rightarrow \text{oxidative addition} \rightarrow \text{reductive elimination}\)

**Notes:**

\(\text{The “templating” aliphatic nitrogen atom is circled. Possible ancilliary ligands omitted for clarity.}\)
A selection of solvents, copper salts, bases, and 1,3-dicarbonyl ligands were screened for the cyclization of Scheme 3. Scope of Substrates for the Formation of Substituted N-Methylated Dibenzo[1,5]oxazocines

\[ \text{Cul (5 mol %) TMHD (10 mol %) Cs}_{2} \text{CO}_{3} (2 \text{ equiv}) \]
\[ \text{Sodium ascorbate (10 mol %) Sodium sulfate (2 equiv) } \]
\[ \text{CH}_{3} \text{CN, 120 °C, \mu W, 5 h, 84%} \]

seven-membered derivative 22 could be generated from substrate 23 in a high yield (Scheme 4).\(^{15}\) Nine-membered rings (24 and 25) could also be obtained using the optimized conditions (from 26 and 27 respectively), albeit with a reduced yield (Scheme 4). Heterocyclic functionality was incorporated into one product, 25, further demonstrating the value of the methodology in the context of the generating pharmaceutically relevant products.

The attempted ring closing of secondary amine 10 to 28 failed under the optimized cyclization conditions. However we have developed an alternative route to 28 (Scheme 5). An allyl group is easily appended to the secondary nitrogen of 10 to give 29. Cyclization then proceeded smoothly to generate 30. The allyl group was removed in high yield using Wilkinson’s catalyst, thus furnishing 28. The amine of 28 provides a handle for further functionalization around the biaryl core.

We hypothesize that the success of these cyclization reactions is due to the presence of a “templating” nitrogen atom in the acyclic substrates, which chelates the copper catalyst and thereby facilitates ring-closure. Consequently, it was expected that acylation of the templating nitrogen would diminish the reactivity of the system, since the lone pair of electrons could then be delocalized into the carbonyl bond and thus would not be as available for co-ordination to a copper species. Indeed, it was found that

\(11\) See the Supporting Information for details regarding the optimization studies.

\(12\) The use of this ligand in the formation of diaryl ethers has previously been reported. See, for example: Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. F.; Reider, P. J. Org. Lett. 2002, 4, 1623.

\(13\) There was no evidence of any competitive intermolecular couplings, despite the relatively high concentration used. Medium ring formations from acyclic precursors frequently require the use of more dilute reaction conditions. See ref 6 and references cited therein.

\(14\) The reaction of 7 to 12 (Scheme 2) proceeds in 74% yield at 80 °C in the absence of both the sodium ascorbate and sodium sulfate. Microwave heating to 120 °C and addition of sodium ascorbate were both shown to increase the yield of this reaction. Further research into the basis for this effect is ongoing. The addition of sodium sulfate was found to have a minimal impact upon the maximum yield obtained for this cyclization. However, in the absence of sodium sulfate, the yields for this process were found to be quite variable and observed to change with the age of the cesium carbonate base used. This effect was ascribed to the variable moisture content of the base, and the addition of sodium sulfate (which presumably acts as a drying agent) was found to improve the reliability of the reaction.

\(15\) As seven-membered ring formation is often faster than for equivalent eight-membered rings, we sought confirmation that the aliphatic chelating nitrogen was still playing a part in facilitating the cyclization process. To that end we synthesized an all carbon equivalent of the acyclic precursor leading to 24 and subjected it to the optimized cyclization conditions. As expected, there was no evidence for the formation of the corresponding cyclic product (see the Supporting Information for synthesis details).
We decided to investigate whether addition of a further amine could restore reactivity (Scheme 6).

Gratifyingly, exocyclic amine functionality tethered via an aliphatic linkage to the linear substrate (compound 32) allowed successful cyclization to form 33. We propose that this exocyclic tether is flexible enough to bind the copper. It is striking that this proposed 11-membered chelate is able to so dramatically affect the coupling process. Conceivably, this “remote activation” concept could be leveraged in the synthesis of alternative series of oxidized dibenzoxazocine-type scaffolds, extending the scope of the cyclization strategy.

In conclusion, we have developed a new, concise, and general protocol for the synthesis of compounds based around tricyclic biaryl ether-linked scaffolds incorporating seven-, eight-, and nine-membered ring amines, including the dibenz[b,g][1,5]oxazocines class of heterocycles. The process displays a broad substrate scope, uses an inexpensive copper catalyst, and generates rare and biologically interesting heteroaromatic products that would be difficult to synthesize by other methods. We envisage that this approach should prove useful for the exploration of hitherto under-investigated scaffolds and thereby the discovery of new molecules of medicinal interest. Compounds synthesized in this program are currently being screened for biological activity. Further mechanistic investigation is underway in our laboratories to clarify the activating effect of the “templatting” nitrogen. The results of these studies will be reported in due course.

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**Supporting Information Available.** Experimental procedures, characterization data, and 1H and 13C NMR spectra.

The authors declare no competing financial interest.