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Dearomatizing spirocyclization reactions of alkynyl cyanamides

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ABSTRACT

Electrophile-induced dearomatizing spirocyclization reactions of propargylic cyanamides leading to cyclohexadienone derivatives are described. An unusual one-pot spirocyclization-N-cyanation reaction has been discovered leading directly to the spiro fused derivative. The products obtained through this chemistry may serve as key intermediates in synthetic approaches to several *Leucetta* alkaloids.

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Figure 1: Representative examples of the *Leucetta* alkaloids

Our group has an ongoing interest in the development of synthetic methods for the construction of imidazole-containing alkaloids belonging to the *Leucetta* family (Figure 1).¹ In general terms our strategy has involved the elaboration of relatively simple imidazoles to substrates resembling nominal biosynthetic intermediates and then using bioinspired approaches;² this approach has served us well in the context of a significant number targets (**1-8**, Figure 1).³ However accessing other members through this strategy, e.g., the spirocalcaridines **9** and **10**, has remained elusive and accordingly we have begun to evaluate complimentary approaches involving the *de novo* synthesis of the heterocyclic core.⁴ Specifically, guided by reports from the Looper⁵ and van der Eycken⁶ labs as inspiration, we have explored cyclization reactions of propargyl guanidine derivatives. As part of this investigation, we have examined the conversion of *N*-methyl propargylamines to the corresponding cyanamide and uncovered an unexpected dearomatizing spirocyclization reaction upon reaction with cyanogen bromide. In this Communication, we describe this observation, along with other electrophile induced dearomatizing spirocyclization of a propargyl cyanamide with more traditional reagents.⁷

As noted above, we modeled our investigation on precedents from the Looper⁵ and van der Eycken⁶ labs wherein the requisite propargylic amines **15** were prepared through a three component coupling between known aldehyde **13**, *N*-methyl allylamine and the copper acetylide (formed *in situ*) derived from 4-ethynylanisole to afford **14** (Scheme 1). Deallylation of **14** with Pd(0) and barbituric acid resulted in the formation of the secondary amine **15**. At this stage, our plan was to convert the amine into the corresponding cyanamide **17** and use that as a divergence point to access a variety of guanidines. In an initial experiment, amine **15** was treated with excess cyanogen bromide in the absence of base resulting in the formation of a new species. It was clear from the ¹H and ¹³C NMR data that the expected

cyanamide **17** was not formed as there were characteristic signals for a cyclohexadienone moiety and in fact the patterns were completely consistent with the formation of a spiro fused system.^{4, 8} IR data clearly supported this analysis through the presence of a carbonyl signal at $\nu_{C=O} = 1661 \text{ cm}^{-1}$, but more intriguingly, there was a signal at $\nu_{C\equiv N} = 2209 \text{ cm}^{-1}$, consistent with the incorporation of a cyano group. At this stage our working hypothesis was that a product derived from electrophile-induced dearomatizing spirocyclization had formed.⁸ Based on the spectroscopic data and the intrinsic polarization of cyanogen bromide we were leaning towards a structure in which the cyano group had triggered the dearomatizing spirocyclization. However, in contradiction to these results from the spectroscopy, mass spectrometry data indicated that the molecule contained bromine **and** a cyano moiety. Fortunately, the compound produced crystals suitable for X-ray crystallographic analysis which showed that bromine had triggered the spirocyclization and that the cyanide had been incorporated as a cyanamide moiety as initially required, producing **16** (Scheme 1).⁹ Interestingly, when the reaction is conducted in the presence of potassium carbonate as base the expected cyanamide **17** is produced in good yield.

Scheme 1: Unexpected dearomatizing spirocyclization

The formation of the spirocyclic compound under these reaction conditions was a somewhat surprising but potentially useful outcome in the context of several planned total synthesis projects. As we thought about the potential mechanistic pathways for this transformation, one possibility we considered was that cyanogen bromide was serving as an electrophilic source of bromine. To test this hypothesis, we subjected two substrates **18** and **19** (Figure 2), which are known to undergo dearomatizing spirocyclization with Br_2^8 or I_2^4 respectively, however, neither alkyne underwent reaction upon treatment with cyanogen bromide. Similarly, exposure of cyanamide **17** to cyanogen bromide did not result in a spirocyclization reaction either (Scheme 2).

Figure 2: Two unreactive substrates with cyanogen bromide

Based on these observations, we suspected that molecular bromine was being formed *in situ* and it was this that served as the electrophilic trigger. While not diagnostic, the reaction mixture took on the characteristic red-brown color of bromine. To test this notion, we subjected cyanamide **17** to reaction with several electrophiles that are known to induce dearomatizing spirocyclization. Gratifyingly, the same spirocyclohexadienone **16** was obtained on treating **17** with NBS in acetonitrile in approximately the same yield as with cyanogen bromide (Scheme

2). Similarly, reactions with NIS and molecular iodine delivered the corresponding iodo-substituted derivative in similar yields. Attempts to extend the cyclization to other electrophiles were partially successful. For example, subjection of cyanamide **17** to reaction with phenylselenenyl bromide resulted in the formation of the selenium-substituted spirocycles **22** in good yield, but in contrast reaction with phenylsulfenyl bromide (formed *in situ* from PhSH/NBS or $(\text{PhS})_2/\text{Br}_2$) delivered a separable mixture of bromide **16** and the protonated congener **23** rather than the desired sulfenylated derivative **21** (Scheme 2). In earlier work, we reported that even acids will promote this dearomatization, accordingly, we exposed **17** to TFA.^{4, 10} Remarkably, even under these conditions a spirocycle **23** was obtained in modest yield along with the dihydronaphthalene derivative **24** (Scheme 3).

Scheme 2: Dearomatizing spirocyclizations of cyanamide **17**

Scheme 3: Acid-mediated dearomatizing spirocyclization

As a control reaction, we exposed the *N*-methylamine **15** to reaction with NBS and found that it did not produce the corresponding spirocyclic amine, presumably due to competitive *N*-bromination. Based on this result, as well as the others described above, we propose the following sequence for the formation of the spirocycle (Scheme 4). The cyanamide **17** forms in the normal way and then activation of the triple bond with bromine then triggers the dearomatizing spirocyclization. The origin of the formation of bromine presumably arises from the reaction of HBr formed in situ with cyanogen bromide through displacement of cyanide. Support for this hypothesis came in the form of control reactions where Br₂ (0.1 equiv.), HBr (0.1 equiv.) or Br[−] (0.1 equiv.) were added to the reaction of **17** with cyanogen bromide. In the cases of Br₂ and HBr the spirocyclic product **16** was obtained in good yield, in the latter case this was accompanied by the formation of the dihydronaphthalene derivative through a cyclohexadienone-phenol rearrangement. Whereas either inorganic bromide (NaBr) or organic bromide (TBABr) failed to initiate the reaction.

Scheme 4: Putative mechanism for the conversion of the *N*-methylamine into the corresponding spirocyclic derivative through the action of cyanogen bromide.

In summary, we have found divergent reactivity of an *N*-methyl propargyl amine with cyanogen bromide resulting in the formation of a dearomatized spirocyclic product in the absence of base but the expected cyanamide is formed in the presence of base. Subsequently, it was demonstrated that the cyanamide is a competent substrate in the electrophile-initiated dearomatizing spirocyclization with halogens, sulfur and selenium but not with cyanogen bromide. The latter observation, coupled with other

control reactions, suggests that bromine is formed *in situ* under non-basic conditions and it is this that triggers the spirocyclization. To the best of our knowledge the reactions reported in this communication constitute the first examples of electrophile-induced dearomatizing spirocyclizations of propargylic amines. The polyfunctional derivatives prepared in the course of this investigation may serve as key intermediates en route to several *Leucetta* alkaloids, these efforts will be disclosed in due course.

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