Tetrahedron Letters 57 (2016) 3096–3099

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Dearomatizing spirocyclization reactions of alkynyl cyanamides

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ARTICLE INFO

Article history:
Received 3 May 2016
Revised 25 May 2016
Accepted 27 May 2016
Available online 28 May 2016

Keywords:
Cyanogen bromide
Cyclohexadienone
Leucetta alkaloids
Total synthesis
Electrophile-induced

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.

Our group has an ongoing interest in the development of synthetic methods for the construction of imidazole-containing alkaloids belonging to the *Leucetta* family (Fig. 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 of targets (**1**–**8**, Fig. 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 Looper[5] and van der Eycken[6] 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 Looper[5] and van der Eycken[6] 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 ^{1}H and ^{13}C 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 cm^{-1}, but more intriguingly, there was a signal at $\nu_{C\equiv N}$ = 2209 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 toward 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.

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http://dx.doi.org/10.1016/j.tetlet.2016.05.104
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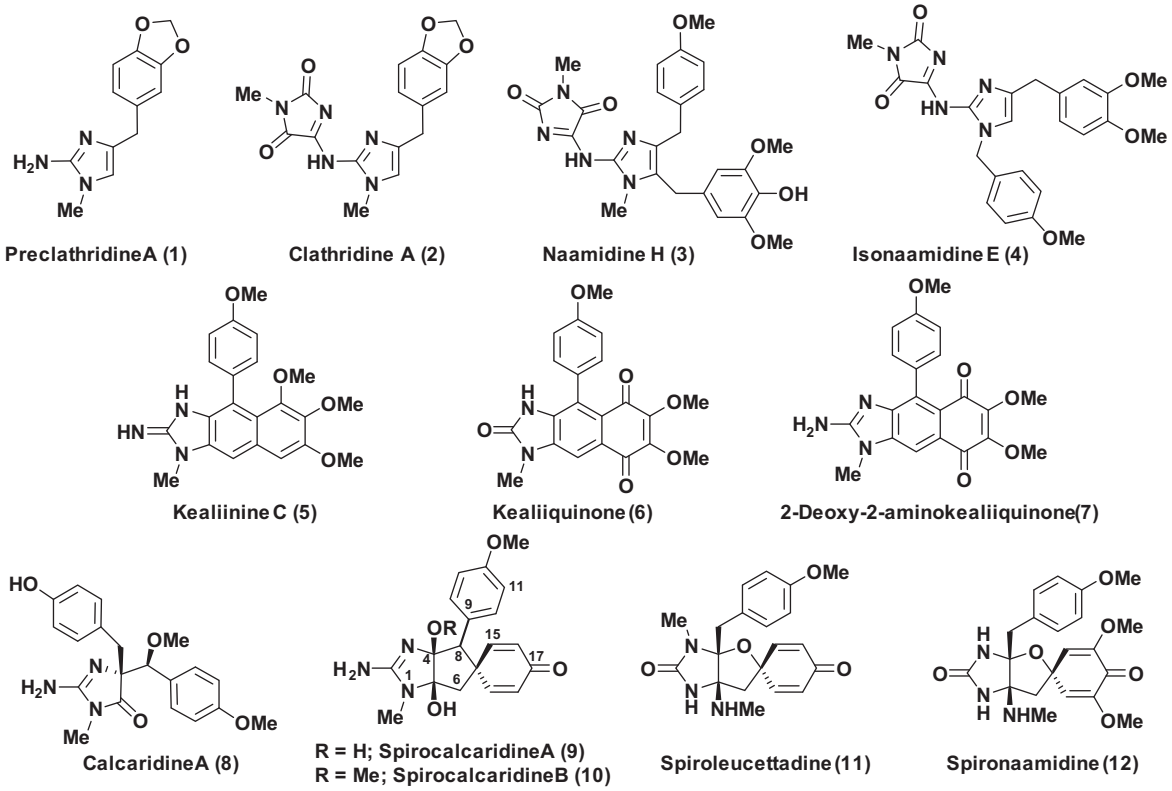
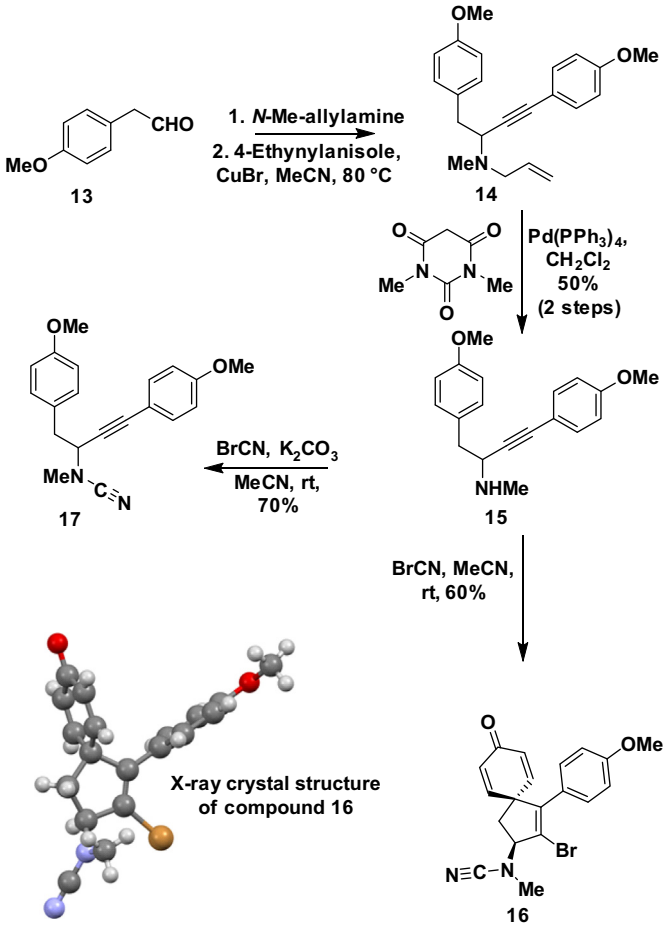


Figure 1. Representative examples of the *Leucetta* alkaloids.



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** (Fig. 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).

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

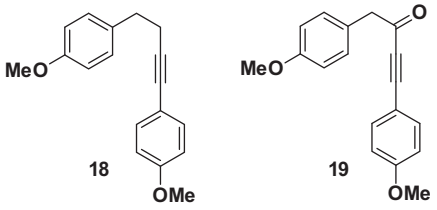


Figure 2. Two unreactive substrates with cyanogen bromide.