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Tandem Oxidative Dearomatizing Spirocyclizations of Propargyl Guanidines and Ureas

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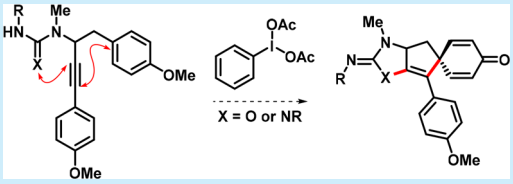
Supporting Information

ABSTRACT: Treatment of propargyl ureas or guanidines with iodosobenzene diacetate results in an oxidative tandem amination/etherification dearomatizing spirocyclization. This transformation leads directly to the complete framework of the *Leucetta* alkaloids, spirocalcaridine A and B.



In a project directed toward the total synthesis[1] of two members of the *Leucetta* alkaloids,[2] spirocalcaridine A (**3**) and B (**4**),[3] we have reported high-yielding approaches to the spirocyclic system[4] based on a Larock-type electrophile-induced dearomatizing spirocyclization (i.e., Figure 1a, E = I)[5] through

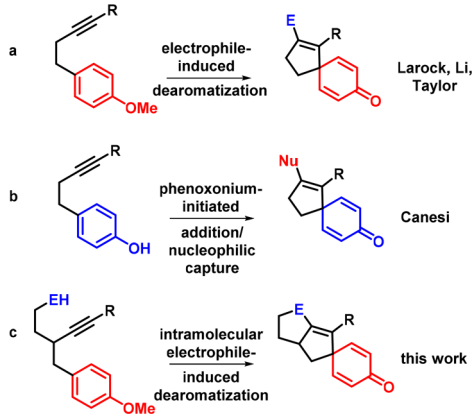


Figure 1. Modes of dearomatizing spirocyclizations.

formation of bond b (Figure 2).[6] Attempts to elaborate these intermediates through annulation of the imidazole, resulting from the formation of bond a (Figure 2), have not been successful in our hands to date. However, the facility of the dearomatizing spirocyclization[7] to construct the BC rings encouraged us to explore this chemistry further. Specifically, we wished to establish whether there was a possibility of configuring the system such that both the spirocyclization (bond b formation) *and* the imidazole formation (bond a formation) would occur in one synthetic operation. As indicated in Figure 2, oxidation of either the phenol (phenoxonium, **5** site b)[8] or guanidine (nitrenium, **5** site a)[9] could trigger the reaction with the only (nominal) difference being the direction of the sequence.[10]

Given the large number of examples of phenolic oxidations (route b) reported in the literature,[7b,c,11] we chose to evaluate this approach first. In particular, chemistry by Canesi and co-

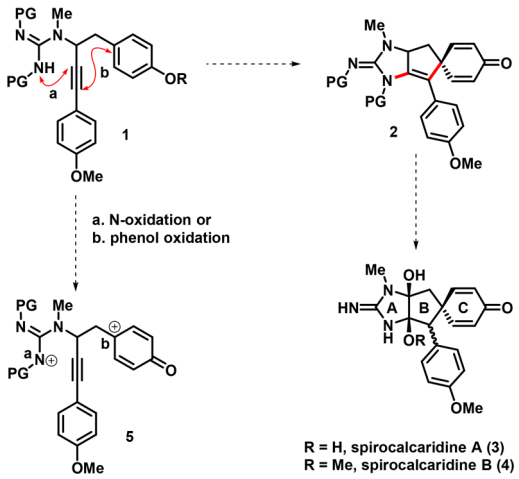


Figure 2. General approach to spirocyclic *Leucetta* alkaloids.

workers involving trapping of alkynes with phenoxonium ions was especially encouraging (Figure 1b).[12] The requisite substrate **12** was assembled via chemistry described by Looper[13] and van der Eycken[14] through a Mannich-like reaction between aldehyde **6**, allylic amine **7**, and the copper acetylide derived from anisyl acetylene **8** and copper bromide (Scheme 1). Deallylation with $Pd(PPh_3)_4$ and *N*,*N*′-dimethylbarbituric acid (DMBA) provided secondary amine **10** which upon treatment with the bis BOC-protected isothiourea **11** and mercury oxide delivered the protected guanidine **12**. Fluoride-induced desilylation then afforded the required phenol substrate **13** for oxidation. The phenol was reacted with IBDA (iodosobenzene diacetate) to initiate reaction via the formation of the phenoxonium ion. A complex mixture of products was formed from which two cyclohexadienones were isolated in poor yield (Scheme 1). It was clear from the characterization data that they were indeed tricyclic products. The ^{13}C NMR spectra were particularly

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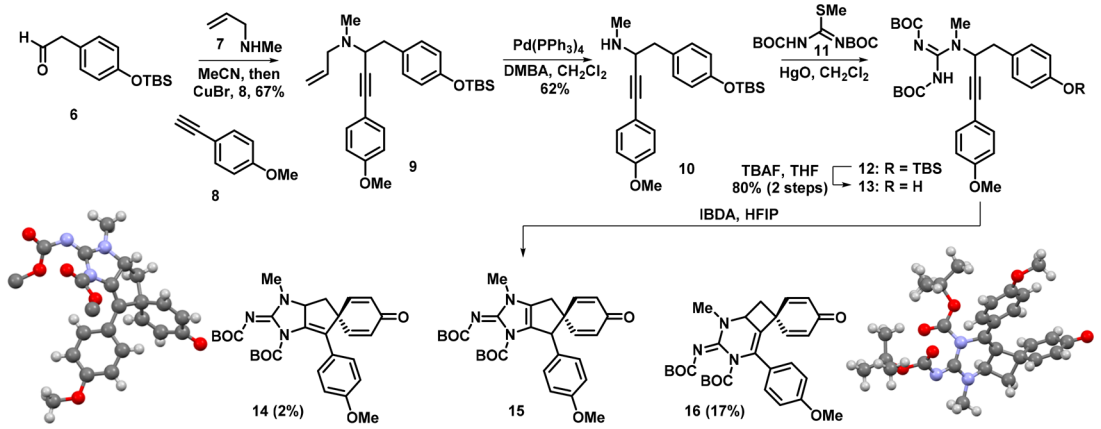
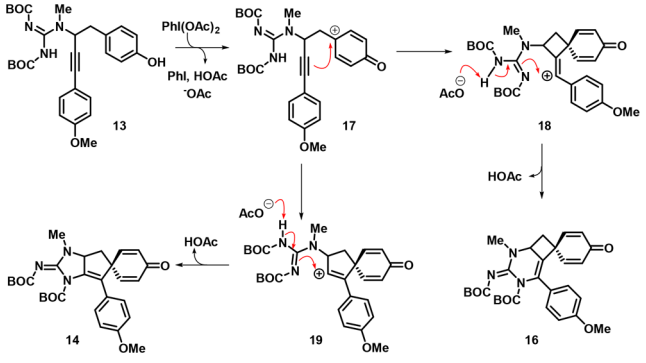
Scheme 1. Preliminary Scouting Experiments and X-ray Structures of Compounds 14 (Methyl Groups on t-BOC Groups Removed for Clarity) and 16



diagnostic in which signals consistent with the quaternary spirocyclic carbon (δ_C = 45.7) and the conjugated ketone (δ_C = 185.5) were observed. Thus, on the basis of these data, the structures were assigned tentatively as the initial cyclization product **14** and a product **15** where olefin migration had occurred. Subsequently, X-ray crystal structures were obtained on both of the isolated compounds from this transformation. The minor product **14** was shown to be the expected cyclization product derived from a 5-*endo-dig* pathway, whereas the major product **16** contained a vinylidene cyclobutane framework arising from a 4-*exo-dig* pathway. It had been expected that the five-membered ring would be formed preferentially, but on closer analysis of the putative intermediates **18** and **19** (Scheme 2), the formation of vinylic carbocation **18** would appear to be more stabilized through a resonance interaction than the corresponding cyclopentenyl cation **19**.

Scheme 2. Mechanistic Overview of the Dearomatizing Spirocyclization Reaction



Given these initial observations with the phenoxonium pathway, the corresponding system which would proceed via the putative intermediacy of the nitrenium ion was evaluated. Preparation of the substrate was accomplished in a largely analogous fashion from the methoxy-substituted aldehyde **20** through a three-component coupling reaction (Scheme 3). Deallylation of **21** provided the secondary amine **22** in good yield. In an initial experiment, it was decided to prepare and evaluate ureas as this would facilitate scouting experiments. Thus, upon treatment of **22** with phenyl isocyanate the *N*-phenyl urea **25** was obtained. Subjection of **25** to oxidation with IBDA in hexafluoroisopropanol (HFIP) (Scheme 3, Table 1, entry 1) delivered a single product in good yield; NMR data showed clearly that dearomatization had taken place. However, it was not immediately clear whether cyclization had occurred through the urea nitrogen as desired for total synthesis applications or through oxygen. Gratifyingly, the material was sufficiently crystalline to obtain an X-ray crystal structure of the product which clearly revealed that the reaction had occurred via oxygen to produce the 2-iminooxazole **31**. On the basis of this initial result, optimization of the reaction was undertaken and is reported in Table 1. Addition of base improved the yield and conversion of the process (Table 1, entries 2−7), Cs_2CO_3 being particularly effective (Table 1, entry 2), although KOH was equally effective. Organic bases (entries 6 and 7), although effective, did not lead to significant improvements. HFIP proved to be the only solvent evaluated (entries 2, 8−10) in which the reaction proceeded in delivering the spirocyclic product. Interestingly, in TFE, a different product was observed, specifically a dihydronaphthoxazole (Table 1, entry 8).[15,16] Two other iodosobenzene oxidants were examined (entries 13 and 14) but these resulted in no improvement, and thus, the conditions identified in entry 2 were used in subsequent reactions.

With conditions identified for the tandem dearomatizing spirocyclization, the substrate scope and limitations were investigated. Accordingly, exposure of amine **22** to other isocyanates, including aryl-, benzoyl- and benzyl-substituted congeners, delivered the corresponding ureas **26**−**30**. Oxidation with IBDA provided the 2-iminooxazoles **32**−**36** in good overall yields. Reaction with the chiral isocyanate (R = CHMePh) delivered a 1:1 inseparable mixture of diastereomeric ureas **30** which underwent spirocyclization to produce the corresponding oxazoles **36** also as an inseparable mixture (Scheme 3).

The success of this chemistry with ureas encouraged us to evaluate the corresponding guanidines. These substrates **37**−**39** were simple to prepare by reaction of secondary amine **22** with the corresponding isothiourea **11**, **23**, **24**, and HgO (Scheme 3). Exposure of the BOC-protected guanidine **37** to IBDA and 1.5 equiv of Cs_2CO_3 resulted in the smooth conversion of the propargylguanidine into the previously synthesized spirocyclic derivative **14** in excellent yield. Similarly, the CBZ- and TEOC-protected guanidines **38** and **39** underwent dearomatizing spirocyclization to deliver the corresponding cyclohexadienones **40** and **41** in good yields.

Mechanistically, we envision that the process begins by the IBDA activation of the urea oxygen or the guanidine nitrogen

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Scheme 3. Oxidative Etherification and Oxidative Amination Dearomatization Spirocyclization

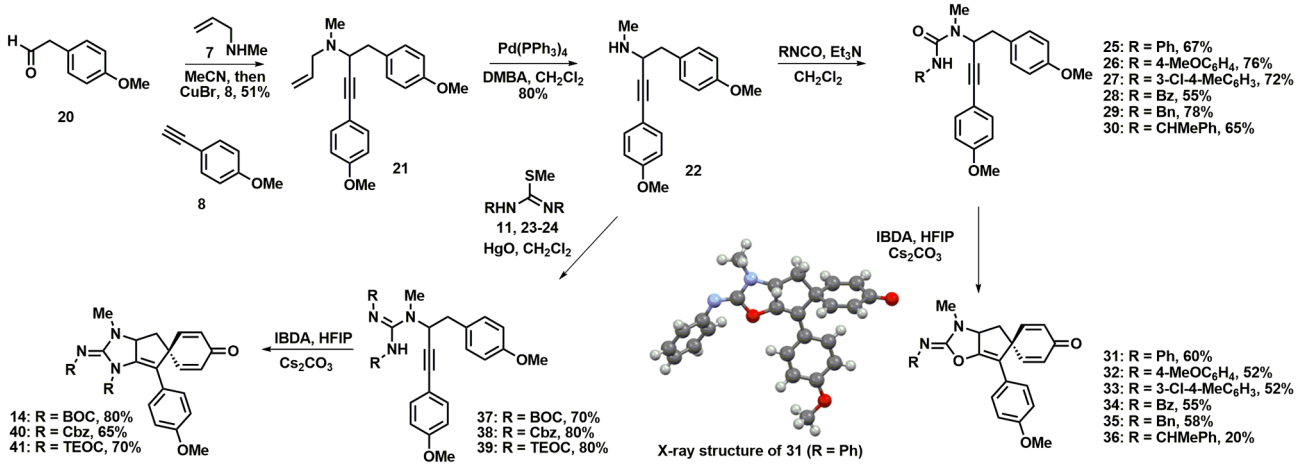
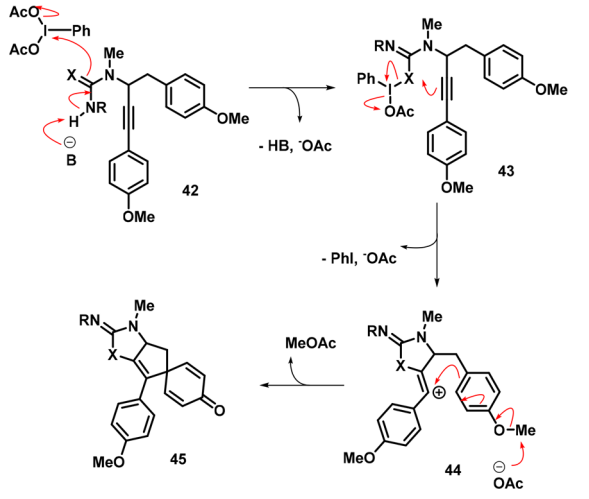


Table 1. Initial Reaction Screening Using Propargyl Urea 25[a]

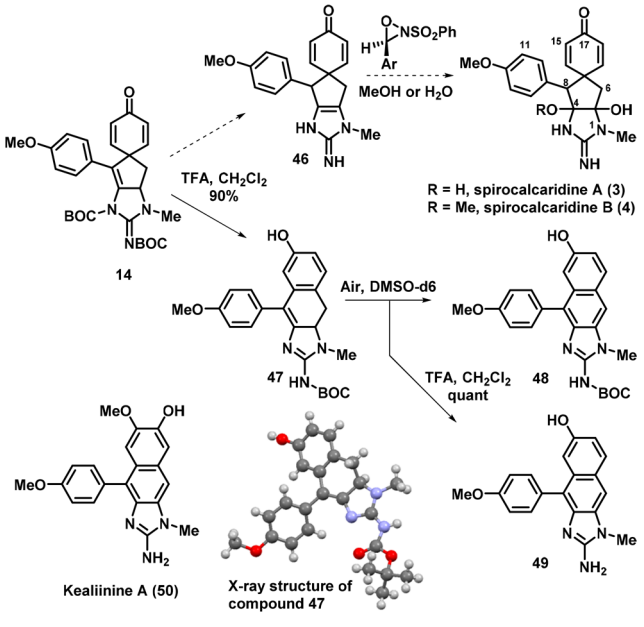
entry	oxidant	base	solvent	time (h)	yield[b] (%)
1	$PhI(OAc)_2$		HFIP	1.5	75
2	$PhI(OAc)_2$	Cs_2CO_3	HFIP	1.5	90 (60)
3	$PhI(OAc)_2$	K_2CO_3	HFIP	1.5	87
4	$PhI(OAc)_2$	KOH	HFIP	1.5	90
5	$PhI(OAc)_2$	NaOH	HFIP	1.5	80
6	$PhI(OAc)_2$	Et_3N	HFIP	1.5	80
7	$PhI(OAc)_2$	DBU	HFIP	1.5	75
8	$PhI(OAc)_2$	Cs_2CO_3	TFE	16	72 (54)[c]
9	$PhI(OAc)_2$	Cs_2CO_3	MeCN	16	NR
10	$PhI(OAc)_2$	Cs_2CO_3	CH_2Cl_2	16	NR
11	$PhI(OAc)_2$	Cs_2CO_3	HFIP[d]	1.5	85
12	$PhI(OAc)_2$	Cs_2CO_3	HFIP[e]	1.5	74
13	$PhI(TFA)_2$	Cs_2CO_3	HFIP	1.5	78 (55)
14	$PhI(OPiv)_2$	Cs_2CO_3	HFIP	2	72

[a]Oxidant was added in one portion to a stirred solution of **25** (1 mmol/30 mL) and base (1.2 equiv) at room temperature. [b]Yield of **31** based on integration data obtained by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard; isolated yields in parentheses. [c]The dihydronaphthoxazole was isolated after 2.5 h on a 0.24 mmol scale. [d]c = 1 mmol/20 mL. [e]c = 1 mmol/10 mL.

Scheme 4. Putative Mechanism of the Tandem Oxidative Dearomatizing Spirocyclization



Scheme 5. Initial Experiments toward the Spirocalcaridines (X-ray Structure of Rearrangement Product 47)



forming the electrophilic species **43** (Scheme 4).[17] Intramolecular addition of the electrophilic heteroatom delivers the vinylic cation **44**, which is then perfectly poised for *ipso* addition to the pendant electron-rich aromatic ring and dearomatization. Demethylation, presumably by acetate anion, then delivers the tricyclic product **45**.

The guanidine products **14**, **40**, and **41** contain the complete skeleton of the spirocalcaridines requiring migration of the C4/C8 double bond to C4/C5, oxidation, and deprotection to complete a synthesis of the natural products (**14** → **46** → **3** or **4**, Scheme 5). An initial attempt to elaborate one of the guanidine derivatives by deprotection of the carbonates was informative of potential challenges to be faced in this approach to the spirocalcaridines. Specifically, treatment of **14** with TFA resulted in the removal of one of the BOC groups but was coupled with rearrangement of the cyclohexadienone into the corresponding hydroxydihydronaphthimidazole **47** (Scheme 5), the structure of which was confirmed through X-ray crystallography.[6a] Intriguingly, this material upon standing in DMSO-d_6 for a few days underwent air oxidation to produce a mixture of the corresponding naphthalene **48** and the dihydronaphthalene **47**.

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While not definitive, these results are suggestive of a possible biosynthetic link between the spirocalcaridines and the kealiinines (e.g., kealiinine A (**50**), Scheme 5)[1i,6a,13b,15,18] and it is thought that the kealiinines serve as biosynthetic precursors to kealiiquinone/2-deoxy-2-aminokealiiquinone.[1k,18] Treatment of this mixture with TFA led to removal of the BOC group and complete oxidation to deliver naphthimidazole **49**. The deprotection−oxidation sequence could be performed more efficiently through the reaction of **14** with TFA in air over a longer period, which resulted in the direct formation of **49** in a few hours (Scheme 5).

In summary, we have developed a tandem alkyne amination−dearomatization strategy for the rapid construction of complex spiro heterocyclic frameworks. These derivatives may serve as precursors to a variety of natural products belonging to the *Leucetta* family of alkaloids including the spirocalcaridines, the kealiinines, and the kealiiquinones. Efforts toward these ends are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01898.

Experimental procedures and characterization data for all new compounds (^{1}H and ^{13}C NMR) (PDF)
X-ray data for compound **14** (CIF)
X-ray data for compound **16** (CIF)
X-ray data for compound **31** (CIF)
X-ray data for compound **47** (CIF)
FID files (ZIP)

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Notes

The authors declare no competing financial interest.

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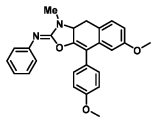
(16) The dihydronaphthoxazole was isolated, which suggests that either spirocyclization is disfavored in this solvent or spirocyclization and rearrangement occur prior to demethylation.



(17) The intermediacy of a discrete guanidine or urea nitrenium ion cannot be ruled out.

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