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Microwave-enhanced, stereospecific ring-closure of medium-ring cyanamide ethers to yohimbine

Nicholas G. Paciaroni, Verrill M. Norwood IV, Daniel E. Garcia, Robert W. Huigens III *

Department of Medicinal Chemistry, Center for Natural Product Drug Discovery and Development (CNPD3), College of Pharmacy, University of Florida, United States

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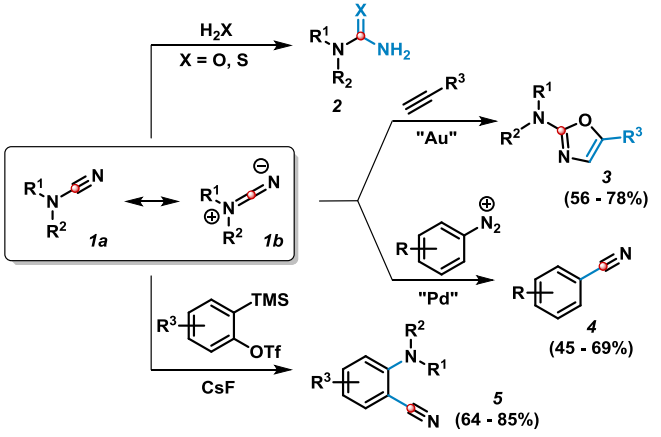
ABSTRACT

A highly efficient acid-promoted, stereospecific, transannular ring-closure of medium-ring ether compounds to the indole alkaloid yohimbine is described. Microwave-enhanced acetic acid degradation of cyanamide compounds involves loss of *(R)*- or *(S)*-ethers, followed by a stereospecific, nucleophilic ring-closure from the cyanamide to afford yohimbine in up to 74% yield in as little as one minute. This nucleophilic reactivity of the amino moiety of the cyanamide highlights an alternative reactivity profile from its traditional electrophilic properties. Additionally, this reaction pathway highlights a rare case of an S_N1 pathway that proceeds with complete stereospecificity.

Introduction

The cyanamide functional group contains both nucleophilic (amine) and electrophilic (nitrile) sites and can be conceptualized as the combination of two major resonance forms (**1a** and **1b**). The polarized nature of the cyanamide enables their use in a bevy of chemical transformations [1–3]. The most traditional uses of cyanamides are condensation reactions with nucleophiles containing acidic protons to generate ureas or thioureas (**2**) via attack on the electrophilic carbon atom (Scheme 1) [4].

The electrophilic nature of the cyanamide carbon atom has also been exploited to yield diversely aminated heterocycles. A gold-catalyzed heterocyclization with terminal alkynes in the presence of an oxygen donor afforded various 2-amino-oxazoles (**3**) [5]. In addition, alternative cyclization reactions have been developed to produce 5-amino oxadiazoles [6], 2-aminobenzimidazoles [7] and oxadizole-5-imines [8]. Diaryl cyanamides (R^1, R^2 = aryl; amine moiety) have found applications in cross coupling reactions by acting as a source for cyanide transfer. Treatment of aryl diazo compounds with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide and catalytic palladium efficiently generates benzonitriles (**4**) [9]. Finally, cyanamides have been utilized for aryne insertion reactions to furnish highly functionalized amino benzonitriles (**5**) [10]. In situ generation of benzyne, followed by nucleophilic attack from the cyanamide amine moiety leads to a highly strained intermediate. Following a carbon–nitrogen bond cleavage of the cyanamide then produces amino benzonitrile products (e.g., **5**).



Scheme 1. Reactivity and transformations of cyanamides.

At the forefront of our group's synthetic campaign in this area was a strategy to selectively cleave carbon–nitrogen bonds around the basic nitrogen of yohimbine (**Y**). One strategy involved the use of cyanogen bromide (CNBr) in an alcohol:chloroform co-solvent (Scheme 2). This allowed us to rapidly produce diverse medium-ring cyanamide ethers via an indole-promoted C—N ring cleavage reaction [11]. Utilizing a variety of alcohol nucleophiles with cyanogen bromide enabled the rapid generation of a sub-library of

* Corresponding author.
E-mail address: rhuigens@cop.ufl.edu (R.W. Huigens III).

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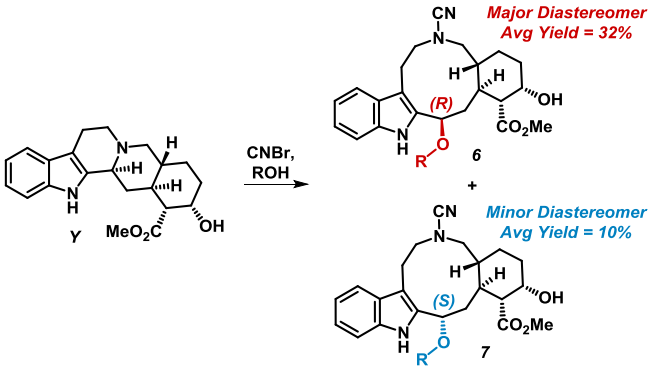


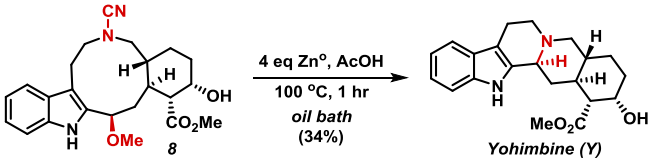
Scheme 2. Synthesis of diastereomeric medium-ring ether cyanamides **6** and **7**.

new compounds for biological evaluation, including major (**6**, average yield = 32%) and minor (**7**, average yield = 10%) diastereomers. The diastereomeric cyanamide ether pairs resulting from this C—N ring cleavage reaction were readily separated via column chromatography.

With initial goals to expand the library diversity of this subset of compounds, we sought to further modify the cyanamide using known hydrolysis conditions to afford the secondary amine for further modification. Cyanamide hydrolysis to the corresponding secondary amine is typically a facile conversion and often employs a Brønsted or Lewis acid [12–14]. However, all attempts to hydrolyze cyanamide compounds (**6**, **7**) to the corresponding amines using trifluoroacetic acid, zinc(II) chloride and aluminum(III) chloride failed. Instead, we observed an unexpected and unprecedented chemical reactivity for the cyanamide functional group, which we report herein.

Results and discussion

Our initial experimental result came from the treatment of cyanamide **8** with zinc(0) in acetic acid for one hour at 100 °C, which resulted in a stereospecific ring-closure to yohimbine **Y** in 34% yield (Scheme 3). This reaction demonstrates a unique reactivity regarding the cyanamide functional group where the amine moiety participated as a nucleophile to perform ring-closure. Intrigued by these unexpected results, we were eager to explore this reaction further by employing microwave (μw) irradiation and eliminating zinc(0). Microwave chemistry offers several benefits to traditional oil bath heating, which include: acceleration of reaction rate via direct microwave absorption of organic molecules, shorter reaction times and higher yields [15–17].



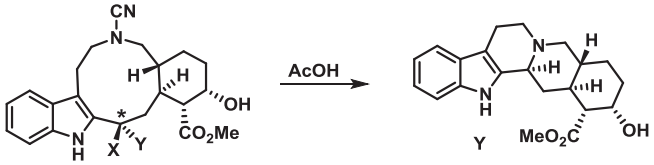
Scheme 3. New acid-promoted cyanamide ring-closure to yohimbine (**Y**).

By utilizing μw irradiation, we were able to isolate yohimbine in 63% yield after five minutes at 160 °C (Table 1, Entry 3). Interestingly, by decreasing the reaction time to one minute, the yield of yohimbine improved to 74% (Table 1, Entry 4). To probe the role microwave heating plays in this process, we ran an analogous reaction using traditional oil bath heating. The oil bath heated reaction required 17 h to complete at 100 °C and afford a lower yield of yohimbine (56% yield; Table 1, Entry 2). This stark contrast in the reaction outcome highlights the need of μw heating regarding the optimization of this transformation.

The hydroxyl derivative, as well as both diastereomers of the isopropyl and phenyl ethers, were treated in a similar manner (160 °C under μw irradiation for one to five minutes) and each derivatives produced yohimbine as the sole product in 18–62% yield (Table 1, Entries 5–10). Moreover, the major diastereomers of the isopropyl and phenyl ethers (Table 1, Entries 7 and 9) resulted in higher yields of yohimbine compared to their corresponding minor diastereomer ethers (Table 1, Entries 8 and 10). This result demonstrates a preference regarding the stereochemistry of the starting ether cyanamide; however, each diastereomer leads to the same product (**Y**) via an indole-promoted S_N1 pathway. It is interesting to note that no *epi*-yohimbine was observed for any of the acid-promoted cyanamide ring-closures. This reaction occurs through an indole-promoted expulsion of a protonated ether, followed by nucleophilic attack by the cyanamide amine moiety to rearomatize the indole nucleus.

Despite this S_N1 process, this reaction is stereospecific for the formation of yohimbine. To rationalize the observed stereospecificity, we analyzed a 2-iodobenzyl ether derivative (**9**) in its ground-state orientation via X-ray crystallography (Figure 1) [11]. In the most stable orientation of the medium-ring ether compounds, the cyanamide group points away from the inner, convex face of the central 10-membered ring of **9**. Depicted in Scheme 4, the ether oxygen of **6** is protonated and subsequently eliminated through electron donation from the indole heterocycle to produce

Table 1
Summary of microwave-enhanced, acid-promoted ring closure reactions to generate yohimbine (Y).



Entry	X	Y	Reagents	Temperature (°C)	Time (min, hr)	% Yield
1	OMe	H	AcOH	25	52 hr	0
2	OMe	H	AcOH, *oil bath*	100	17 hr	56
3	OMe	H	AcOH, pw	160	5 min	63
4	OMe	H	AcOH, pw	160	1 min	74
5	OH	H	AcOH, pw	160	5 min	18
6	OH	H	AcOH, pw	160	1 min	50
7	O'Pr	H	AcOH, pw	160	5 min	62
8	H	O'Pr	AcOH, pw	160	5 min	17
9	OPh	H	AcOH, pw	160	1 min	59
10	H	OPh	AcOH, pw	160	1 min	32

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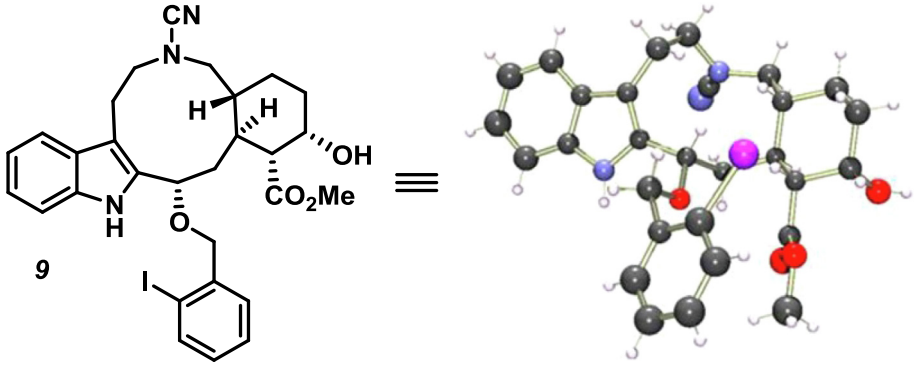
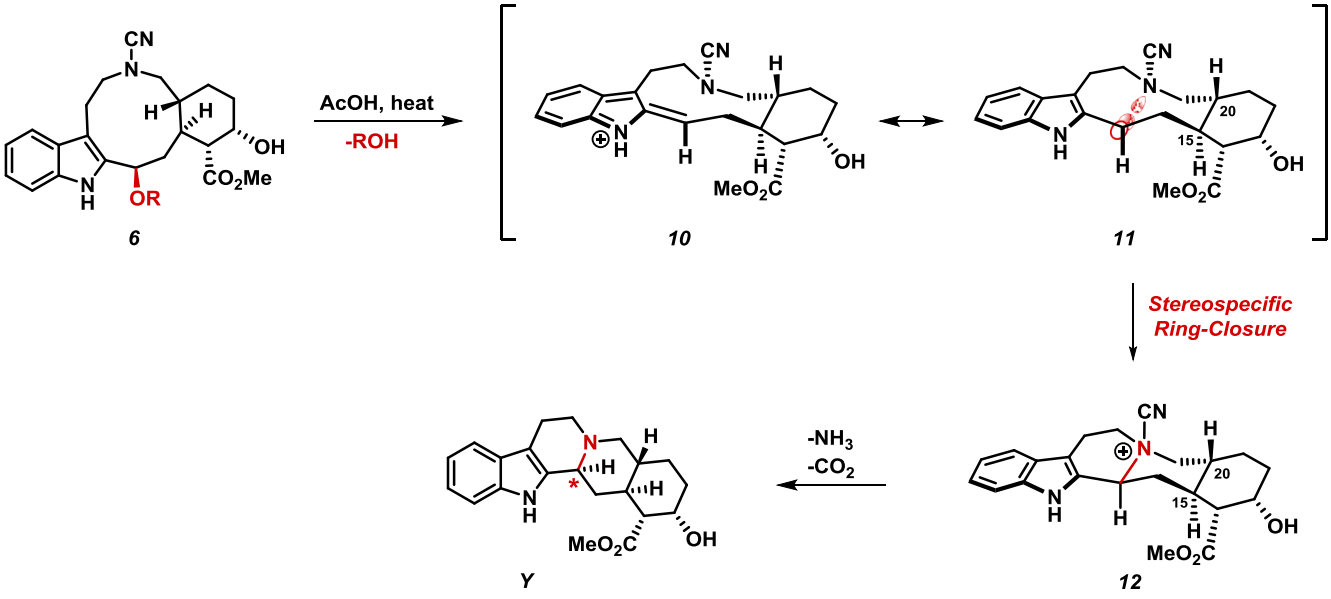


Fig. 1. Structure and X-ray crystal orientation of 2-iodobenzyl ether cyanamide (**9**).



Scheme 4. Mechanistic rationale for the observed stereospecific reaction of the cyanamide transannular ring-closure.

the rigidified, resonance-stabilized carbocation (**10**) [11,18–21]. We believe that the LUMO of the resulting indole-stabilized carbocation (see resonance structure **11**) is appropriately aligned with the orbital lone pair HOMO of the cyanamide nitrogen. This favorable orbital alignment is presumably generated via the *trans*-configuration of the central ring (carbons 15 & 20, Scheme 4) coupled with the rigidified carbocation intermediate, and enables the transannular ring-closure step (**11** to **12**) to proceed exclusively from one face of the reactive intermediate to form yohimbine.

Conclusion

We have discovered an altered reactivity profile of cyanamide-containing compounds which enabled an acid-catalyzed, stereospecific, transannular ring-closure to yohimbine. Cyanamides are known for their electrophilic properties of the nitrile moiety. However, these investigations demonstrate that a range of medium-ring ether cyanamide compounds can undergo an acetic acid-promoted microwave irradiation reaction where the amine moiety of the cyanamide performed a nucleophilic, transannular ring-closure to produce yohimbine. This extremely facile reaction proceeds through an indole-promoted S_N1 pathway and allows for a stereospecific ring-closure to form yohimbine. This reaction pathway exemplifies a rare case where a stereospecific reaction is produced through a S_N1 pathway and we are currently investigating other applications of this unique reactivity in organic synthesis.

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