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Ninhydrin as a building block for yohimbanones, β-carbolines, and oxyprotoberberines

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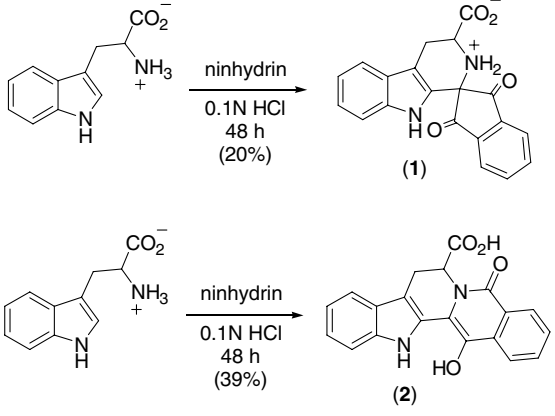
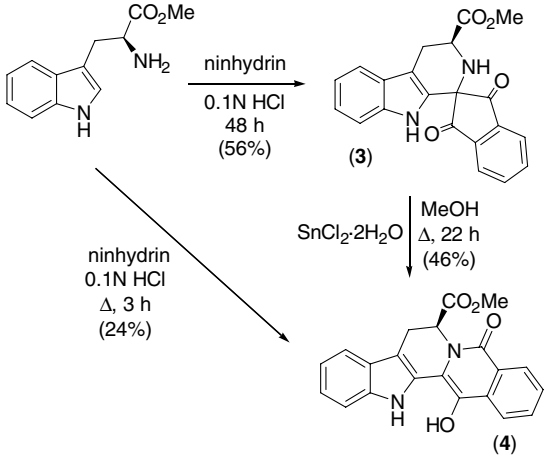
Abstract—Condensation of ninhydrin with tryptamide or tryptamine followed by Lewis acid-induced rearrangement provided yohimbanones that were readily converted to β-carbolines via oxidative ring cleavage. The analogous condensation-rearrangement with 3,4-dimethoxyphenethylamine and ninhydrin afforded an oxyprotoberberine, which was further oxygenated at the 13a position.

While investigating the reactivity of the amino acids with ninhydrin, Heesing et al. discovered that the reaction of tryptophan with ninhydrin did not yield the expected Ruhemann's purple. On the basis of elemental analysis data, they proposed that the yellow solid obtained was a spirocyclic derivative of 1,2,3,4-tetrahydro-β-carboline (**1**, Scheme 1).[1] Nearly 20 years later, Neuzil et al. revisited this reaction and obtained an X-ray structure that identified the product as a yohimbanone derivative (**2**).[2]

Joullié and co-workers investigated the reaction between L-tryptophan methyl ester and ninhydrin and found that a Pictet–Spengler condensation product (**3**), similar to that proposed by Heesing, could be isolated and converted in a separate step to the yohimbanone (**4**, Scheme 2).[3]



Scheme 1. Reaction of tryptophan with ninhydrin.[1,2]



Scheme 2. Preparation of yohimbanone **4** via Pictet–Spengler intermediate **3**.[3]

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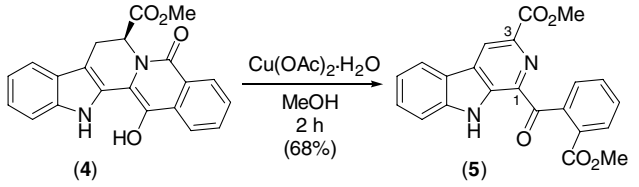
On the basis of these results, it was proposed that the conversion of **3** to **4** proceeds through the attack of the β-carboline nitrogen on the adjacent carbonyl of the indanedione moiety. The resultant hydroxyaziridine intermediate then fragments to produce yohimbanone **4**.[3]

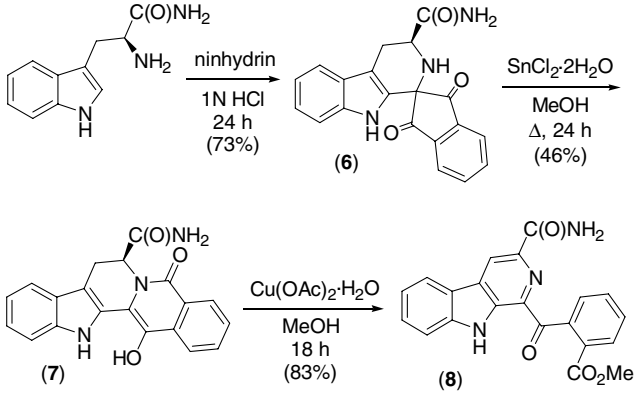
In a subsequent report, Leonard et al. showed that the yohimbanone could undergo oxidative ring cleavage in the presence of cupric acetate to provide a 1,3-disubstituted β-carboline (**5**, Scheme 3).[4] β-Carbolines are of biological interest due to their affinity for the benzodiazepine receptor[5] and anti-HIV activity.[6]

The continuation of our investigation has two goals: (1) the preparation of novel β-carbolines that could be used as molecular probes of the benzodiazepine receptor and (2) the extension of this methodology to other classes of heterocyclic molecules. In addressing the first goal, hydrogen-bonding capability of the C-3 substituent is likely to play a significant role; therefore, an amide-bearing β-carboline (**8**) was prepared in a straightforward fashion from L-tryptamide (Scheme 4).

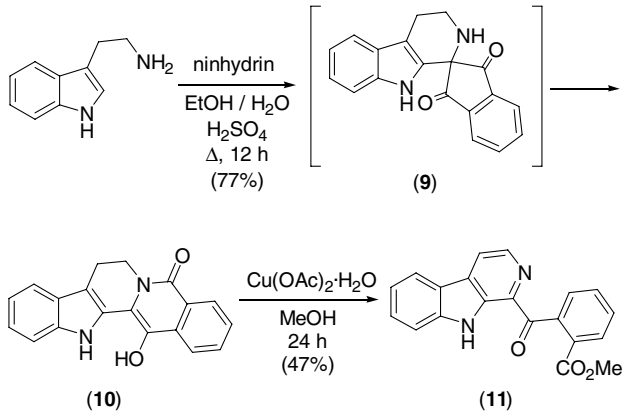
We next attempted to prepare a β-carboline devoid of C-3 functionality (**11**) from tryptamine. Significantly different reactivity was observed in this system. Exposure to Pictet–Spengler conditions resulted in extensive decomposition. Modified reaction conditions[7] did allow for successful condensation to yohimbanone **10**. This approach provides a route to **10** that is complementary to the sequential photochemical cyclization-acidic fragmentation approach of Coyle and co-workers,[8] which provides the yohimbanone in six steps and 15% overall



Scheme 3. Oxidative ring cleavage of yohimbanone **4** to provide β-carboline **5**.



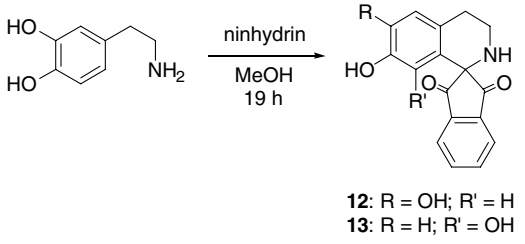
Scheme 4. Preparation of amide-bearing β-carboline **8**.



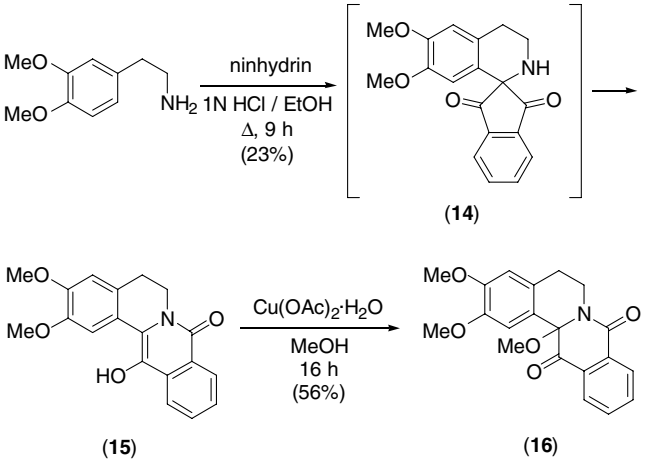
Scheme 5. Synthesis of a β-carboline devoid of C-3 functionality.

yield from phthalimide, tryptamine, and glyoxylic acid.[8e] The spirocyclic tetrahydro-β-carboline (**9**) was a transient intermediate in this series. Oxidative ring cleavage provided the monosubstituted β-carboline **11** (Scheme 5).

We also envisioned that isoquinolines could be prepared from phenethylamine derivatives using a similar approach. Consequently, dopamine was condensed with ninhydrin (Scheme 6); however, an equal mixture of regioisomers **12** and **13** was obtained.[9] Additionally, the subsequent stannous chloride-induced rearrangement was greatly hindered, presumably by the presence of the free phenolic hydroxyl groups.



Scheme 6. Condensation of dopamine with ninhydrin.



Scheme 7. Oxyprotoberberine synthesis.

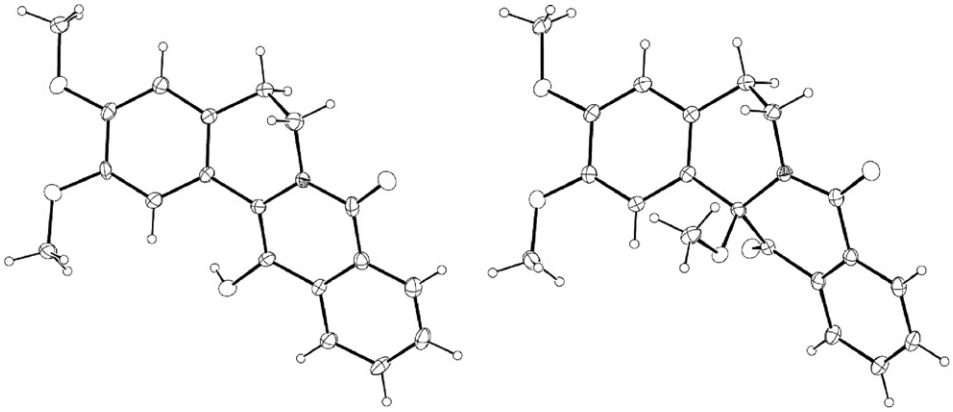


Figure 1. ORTEP drawing of **15** and **16**.

When 3,4-dimethoxyphenethylamine was employed as a reactant, clean conversion to a single regioisomeric product was observed. In this sequence, the Pictet–Spengler intermediate (**14**) was again not isolable, and the oxyprotoberberine **15** was obtained directly (Scheme 7) and verified by X-ray crystallography (Fig. 1). This approach also provides a complement to existing photochemical syntheses.[8d] Upon treatment with cupric acetate, it was expected that oxidative ring cleavage would proceed in an analogous fashion to yield a benzylisoquinoline alkaloid. However, the actual product isolated was oxyprotoberberine **16**.

This product structure was also verified by X-ray crystallography (Fig. 1). Related compounds have been prepared[10] by oxidation of oxyprotoberberines[10a] and acetoxyoxyprotoberberines.[10b] The protoberberines have been the subject of many recent synthetic studies[11] due to their antitumor activities.[12]

This unexpected result may be rationalized by initial oxidation of the structural fragment common to yohimbanones **4**, **7**, and **10** as well as oxyprotoberberine **15**. The highly conjugated and charged intermediate that would result (Fig. 2) could explain the dramatic color change associated with these reactions. Attack of the alcoholic solvent on the lactam carbonyl would lead to ring cleavage, and subsequent spontaneous oxidation provides the observed β-carboline products. Attack of the alcohol on the iminium moiety would provide the addition product observed in the oxyprotoberberine series.

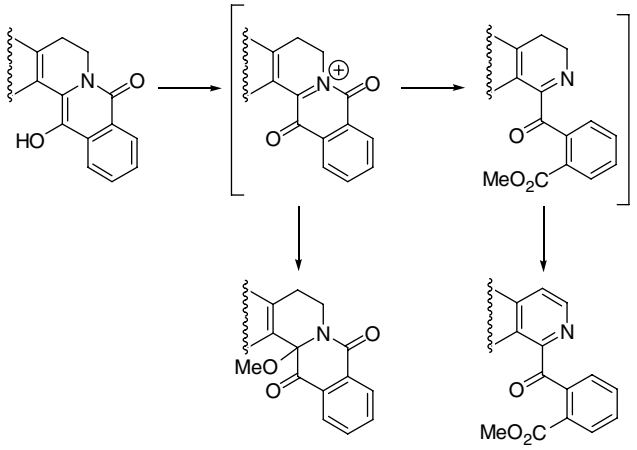


Figure 2. Possible mechanism for divergent pathways.

These results suggest that the concise syntheses of heterocyclic molecules described herein could be finely tuned through substituent effects to allow access to multiple carbon skeletons. The results of screening **5**, **8**, and **11** using Skinner box assays[13] will be reported in due course, as will the application of this methodology to other heterocyclic systems.

Acknowledgments

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Supplementary data

The supplementary data include experimental details for compounds **6**, **7**, **8**, **10**, **11**, **15**, and **16** as well as spectroscopic data. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC 625762 and 625763. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.115.

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