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# A new method for the synthesis of 1,4,5-oxadiazocines and its application in the structure modification of natural products

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**Abstract**—A new method for the synthesis of eight-membered heterocyclic 1,4,5-oxadiazocines has been described from β-diketone and β,β,β-triketone with an acidic α-hydrogen. The method entails the reaction of a di- or triketone with 2-hydroxyethylhydrazine and an aldehyde in the presence of acetic acid providing respectable yield.


Nature has continued to be a rich source for providing structurally diverse small organic molecules that are used as tools to elucidate and interrogate biological functions, sometimes leading to therapeutic agents and clinically useful drugs. The natural products can be highly functionalized and possess multi-functional groups with well-balanced polarity and hydrophobicity with high oxygen content but generally with low nitrogen content which is prevalent in the synthetic drugs.[1] Therefore, chemical and biological methods are often applied to modify these natural products to optimize their activity and physical properties before they can be further developed as a therapeutic agent.

Ilicicolin H (**1**) is a polyketide laced with a variety of functional groups and was isolated from the 'imperfect fungus' *Cylindrocladium iliciola* MFC-870 as a potent antifungal agent.[2] Subsequently, the stereo structure,[3] biosynthesis,[4] and the racemic synthesis[5] were reported. While the antifungal activity of this compound was reported in 1971, its mechanism of action is only now being delineated. It inhibits the yeast cytochrome $bc_1$ complex by interacting at Qn site of the complex.[6] The potent antifungal activity and novel mode of action of this compound attracted our attention and we undertook structural modification of this compound for further improvement of its biological profile. In this report, we wish to describe the chemistry of β-hydroxy ketone (β-diketone that is a part of β,β,β-triketone) that led to the discovery of a new method for the synthesis of rare eight-membered 1,4,5-oxadiazocine ring heterocycles. There exists a vast amount of literature for the synthesis of a variety of heterocycles. However, no significant work has been reported for the synthesis of oxadiazocine heterocycles with exception of a few instances. For example, Guthrie and Honeyman[7] described the synthesis of a substituted oxadiazocine as a structure proof of a 2,3-dialdehyde of a sugar residue, Sparatore et al.[8] reported the preparation of dibenzo-1,4,5-oxadiazocine, Atkinson et al.[9] reported a substituted oxadiazocine as a byproduct of aziridination reaction. Our new method allowed us to introduce two basic nitrogens and an ether oxygen into the β-hydroxy ketone (β-diketone) of ilicicolin H (**1**), forming a new spiro-fused eight-membered 1,4,5-oxadiazocine ring. The generality and synthetic scope of this method was extended with a number of examples.

Ilicicolin H is a potent antifungal agent but lacks in vivo efficacy due to its strong plasma binding. A way to potentially minimize this problem is to modify the molecule's β-hydroxy-ketone motif, which is known for strong chelating properties. Treatment of ilicicolin H with a series of hydrazines afforded the corresponding hydrazones (**2**) which, upon heating with a catalytic amount of acetic acid, cyclized to form the pyrazoles (**3**) (Scheme 1). However, a one-pot reaction of ilicicolin H with 2-hydroxyethylhydrazine in methanol with acetic acid yielded exclusively a separable 1:1 diastereomeric mixture of spiro-fused oxadiazocine derivative (**4**) (Scheme 2) whose structure was confirmed by extensive spectroscopic analysis.[10] In the same reaction, if the

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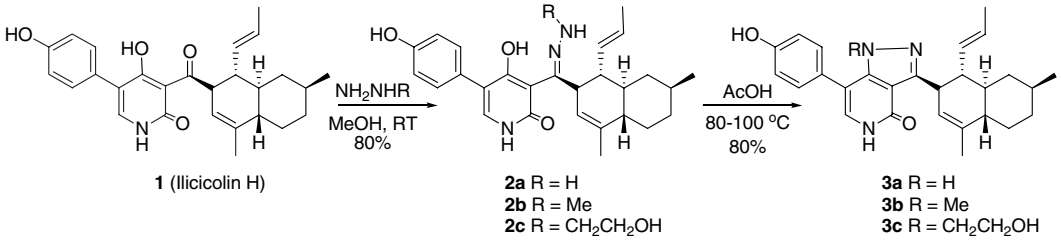
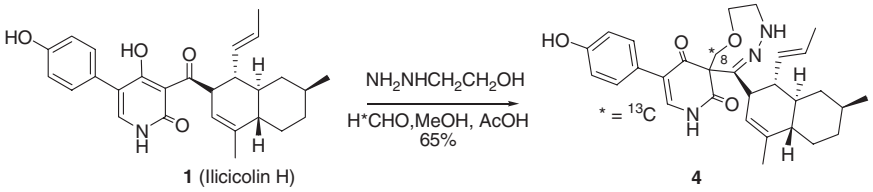



**Scheme 1.** Synthesis of fused pyrazole derivatives of ilicicolin H.




**Scheme 2.** Synthesis of oxadiazocine derivatives of ilicicolin H.

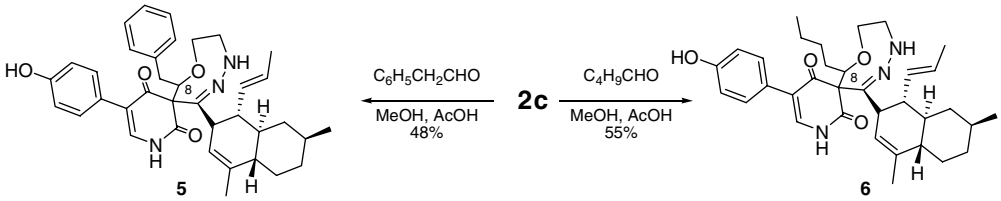
2-hydroxyethylhydrazone intermediate (**2c**) was purified before heating with acetic acid, the fused pyrazole (**3c**) was isolated as the sole product. Since the formation of oxadiazocine requires the incorporation of an extra methylene group, we speculated that the presence of formaldehyde in methanol or in the 2-hydroxyethylhydrazine reagent may have contributed to this new reaction. To confirm this hypothesis, we heated the purified hydrazone intermediate (**2c**) with acetic acid in the presence of small amount of [$^{13}$C]-HCHO, and indeed, isolated the oxadiazocine with $^{13}$C incorporated at C-8 of the oxadiazocine ring (**4** with $*$).

Replacing formaldehyde with other aldehydes such as phenylacetaldehyde and valeraldehyde afforded the oxadiazocines **5** and **6**, respectively, with the corresponding substitutions at C-8 of the oxadiazocine ring. Of the four possible diastereomers, only two were isolated from each reaction. However, attempts to incorporate more hindered aldehyde, such as benzaldehyde and *tert*-butyl aldehyde were not successful (Scheme 3).

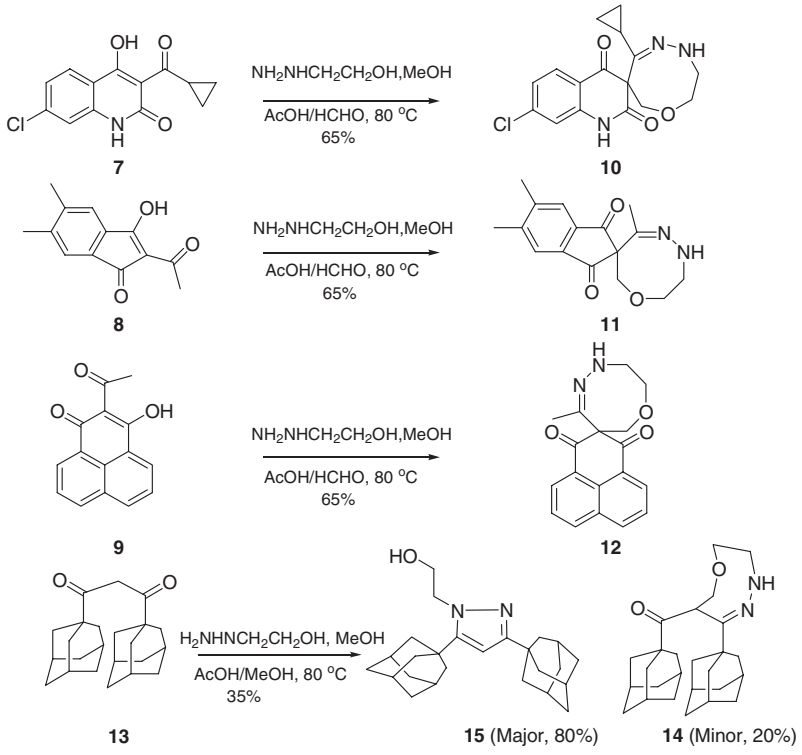
This method of oxadiazocine construction was successfully applied to a few other compounds bearing similar β,β,β-triketone structures as present in ilicicolin H. For example, reaction of compounds **7**, **8**, and **9** afforded oxadiazocines **10**, **11**, and **12**, respectively, in similar 45–65% yields (Scheme 4). However, similar reaction of the diketone **13** afforded only minor amounts of oxadiazocine derivative **14** and major amounts of the pyrazole **15** (Scheme 4). This observation indicated that the ease of the eight-membered ring formation and thus the yield of the oxadiazocines were largely dependent on the acidity of the α-hydrogen of the di and tri-ketone structures and do not appear to be tightly related to the steric factors of the neighboring groups.

Regarding the mechanism of the new method for the synthesis of oxadiazocines, we propose an addition–elimination–addition sequence (Fig. 1). Clearly, the 2-hydroxyethylhydrazone (e.g., **2c**) is the starting material of this reaction. Addition of the hydroxyl group from 2-hydroxyethylhydrazone to the aldehyde gives the hemi-acetal intermediate, which undergoes dehydration under acidic conditions to generate the oxonium ion species. Alternatively, the nitrogen at the hydrazone could attack the hemi-acetal to afford a six-membered enaminium ion intermediate, which is also likely to lead to the oxonium species via the ring opening/closing equilibrium. Although it is tempting to assign the more stable six-membered enaminium ion intermediate as the target for the nucleophilic attack by the enolate, the geometry of those atoms involved (via a four-membered cyclo addition) exclude this possibility. Thus, the oxonium species is the most likely intermediate for the nucleophilic attack giving rise to the eight-membered oxadiazocine ring.

A survey of the literature reveals that large number of such di and tri-ketone structural motifs exist in biologically active natural products (e.g., tenellin,[11] fischerin,[12] apiosporamide,[13] pyridivericin,[14] militarinones,[15,16] and




**Scheme 3.** Synthesis of 8-substituted oxadiazocine derivatives of ilicicolin H.




**Scheme 4.** Examples of 8-substituted oxadiazocine derivatives.

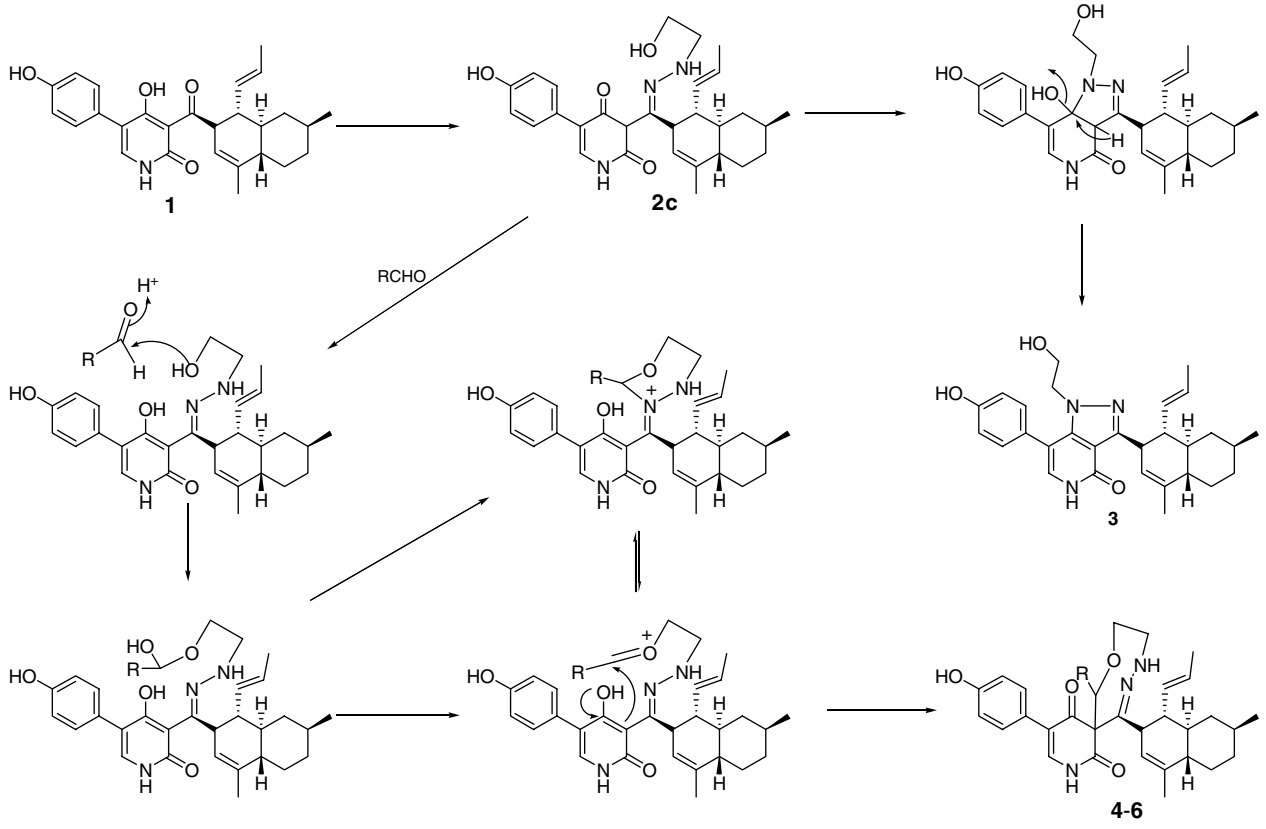



**Figure 1.** Proposed mechanism of the oxadiazocine.

farinosones[17]) as well as synthetic organic compounds. This new method of synthesis of oxadiazocine provides a useful tool for the introduction of nitrogen containing flexible heterocycles in structure modification of natural

products and total synthesis of biologically active organic compounds.

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10. Typical experimental procedure exemplified by synthesis of **4**. To a solution of ilicicolin H (25 mg, 0.057 mmol) in MeOH (2 mL) was added 2-hydroxyethylhydrazine (10 mg, 0.13 mmol, 2.3 equiv) and stirred at room temperature for overnight followed by the addition of formaldehyde (0.2 mL of 37% aqueous solution) and glacial AcOH (one drop). The solution was heated at 80 °C for 4–5 h. After completion (RPHPLC), the product was purified by silica gel chromatography with hexane/ethyl acetate/triethylamine as a solvent system to give diastereomeric mixture of compound **4** (19 mg, 65%) as a free base. Alternatively, the product was also purified by preparative RPHPLC with water/acetonitrile/trifluoroacetic acid as a solvent system to give the corresponding TFA salt of compound **4**. All compounds were fully characterized by 2D NMR and mass spectral analysis.
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