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Unexpected formation of (*Z*)-3-(halomethylene)isoindolinones from *gem*-dihalovinylbenzonitriles: efficient synthesis of enyne-containing isoindolinones

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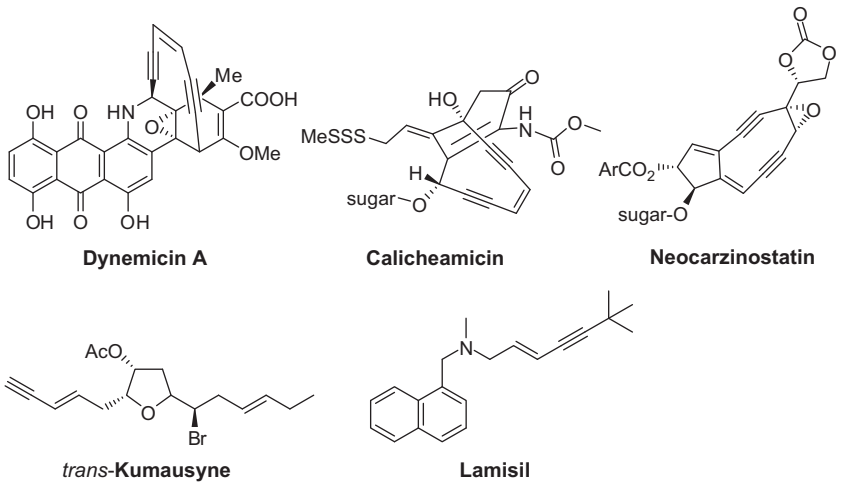
ABSTRACT

An efficient one-pot procedure for the regioselective synthesis of (*Z*)-3-(halomethylene)-isoindolin-1-ones was developed from easily accessible 2-(2,2-dihalovinyl)benzonitriles. From this key intermediate, a variety of isoindolinones containing an enyne moiety were synthesized in good to excellent yields via palladium-catalyzed Sonogashira reaction. The generated enyne-containing isoindolinones could be further manipulated by iodide induced cyclization reaction to afford a versatile synthetic intermediate 5*H*-pyrrolo[2,1-*a*]isoindolol-5-one in high yield and could be further elaborated.

In the past few decades, the conjugated enyne- or enediyne- containing antitumor antibiotics have aroused lots of attention.[1] These molecules act as natural antibiotics destroying the DNA of bacteria and viruses and resulting in the cleavage of DNA,[2] intriguing mode of action,[2b,3] and having extremely potent cytotoxicity to a wide range of tumor cells.[4] In addition to their biological activity, these



Scheme 1. Bioactive products with enyne or enediyne moiety.

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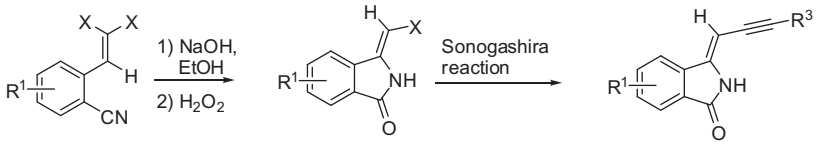
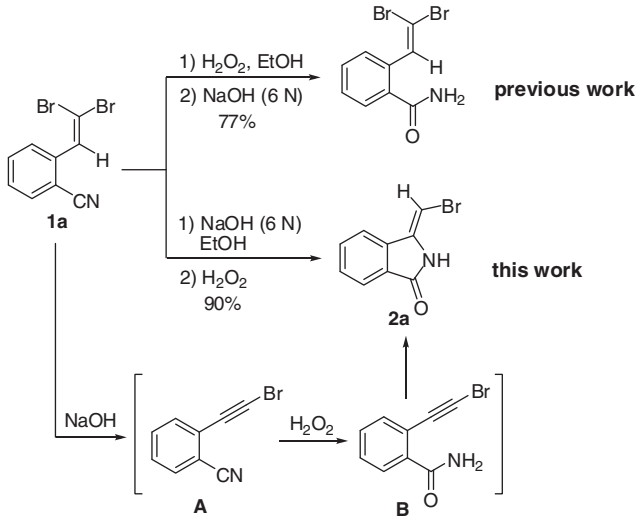
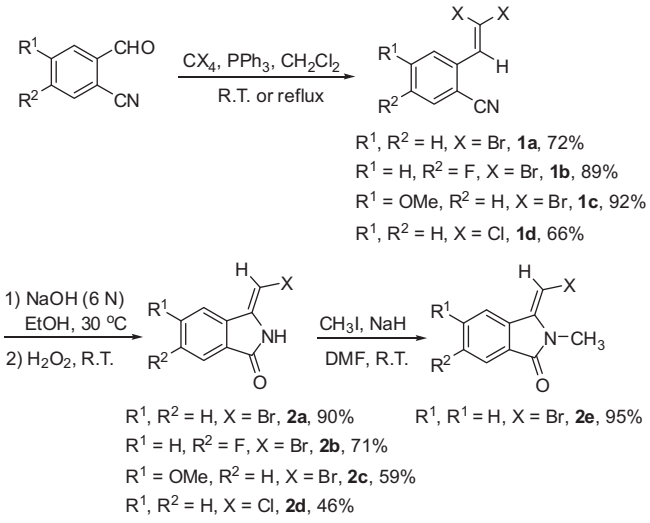


Scheme 2. Synthesis of enyne-containing isoindolinones.



Scheme 3. One-pot synthesis of (*Z*)-3-(bromomethylene)isoindolin-1-one **2a**.



Scheme 4. Synthesis of starting materials.

compounds are also of interest because of their unique structure feature of 1,5-diyne-3-ene or (*Z*)-enediyne which could be used as important synthetic intermediates for chemical transformation.[4] Typical representatives accounting for these characteristics are some nature products, such as Calicheamicin,[5d] Dynemicin A,[5d] *trans*-Kumausyne,[5b] and Neocarzinostatin,[5a,c] and could be exemplified by marketing drugs such as Lamisil that is used for the treatment of onychomycosis of the toenail or fingernail (Scheme 1). Such characteristics have made the molecules significant synthetic targets[6] and, therefore, have resulted in sustained interest in developing new methods for the preparation of this valuable structural unit.[1b]

Special chemical or physical properties have been reported when heterocycles are assembled with enyne pharmacophore.[7] For example, the enyne-containing porphyrinoids present as a new photosensitizer with much better properties which could be widely used in photodynamic therapy (PDT).[7f] When chlorophylls were attached by enyne moiety, they may act as finer donors and acceptors for both energy and charge.[7e] For benzothiophene bearing with a enyne fragment, it becomes a representative allylamine antimycotics, known to act by selective inhibition of the fungal squalnen epoxidase.[7h,i] This discovery sparks a great deal of excitement in the research areas of pharmacology,[7f,g,8] diagnostics,[9] molecular assembly,[10] materials science,[7d,11] artificial photosynthesis,[12] and for the preparation of novel macrocycles.[10]

Isoindolinone derivatives are an important class of heterocycles which could be widely found in both natural products and synthetic pharmaceuticals with fine biological activity.[8,13] They have exhibited a variety of biological activities,[14–16] such as antihypertension,[14g] antipsychotics,[15] antiinflammation,[14f] anesthetic,[16] antiulcer,[14h] and vasodilatory.[14e] In addition, antiviral,[17] antileukemic,[18] and platelet aggregation inhibitory[19] properties have also been observed in this class of structures, as well as acting as useful synthetic building blocks and intermediates in organic synthesis.[13a–e]

Recently, we have developed a novel and efficient one-pot regioselective elimination-cyclization-Suzuki approach to afford (*Z*)-3-arylmethyleneisoindolin-1-ones in good to excellent yields from easily accessible *ortho-gem*-dihalovinylbenzamides and organoboron reagents.[20] (*Z*)-3-(bromomethylene)isoindolin-1-one was proposed as the in situ generated key intermediate in this tandem process. During our research program concerning effective construction and functionalization of nitrogen-containing molecules and biochemical validation of various heterocycles,[21] we intended to prepare the enyne-containing isoindolinones based on the consideration of their potential biological activity. Herein, we reported an efficient synthesis of isoindolinones bearing an enyne scaffold from unusually formed (*Z*)-3-(halomethylene)isoindolin-1-ones which could be derived from *ortho-gem*-dihalovinylbenzonitriles (Scheme 2).

The *ortho-gem*-dihalovinylbenzamides have been prepared by adding aqueous sodium hydroxide into the ethanol solution of 2-(2,2-dihalovinyl)benzonitrile **1a** and hydrogen peroxide (Scheme 3).[20,22] However, when we changed the addition sequence by adding hydrogen peroxide into the ethanol solution of 2-(2,2-dibromovinyl)benzonitrile and sodium hydroxide, the cyclized (*Z*)-3-(bromomethylene)isoindolin-1-one **2a** was predominantly afforded in 90% yield, instead of the previously reported 2-(2,2-dibromovinyl)benzamide (Scheme 3). The formation of this unusual product **2a** was envisioned to assign through dehydrobromination of **1a** under NaOH and furnish the alkynyl bromide **A**,[23] which could be further transferred into intermediate **B** by reacting with hydrogen peroxide.[24] The generated benzamide intermediate **B** will undergo cyclization reaction and lead to (*Z*)-3-(bromomethylene)isoindolin-1-one **2a** sequentially (Scheme 3).[8,20]

To explore the scope of this method, a variety of 2-(2,2-dihalovinyl)benzonitriles **1a–d** were firstly prepared from commercial or readily available substituted 2-formyl-benzonitriles[25] by treating with carbon tetrahalides in the presence of PPh_3 in CH_2Cl_2. The