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Synthesis of 3-(arylmethylene)isoindolin-1-ones from ynamides by Heck–Suzuki–Miyaura domino reactions. Application to the synthesis of lennoxamine

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Abstract—Substituted 3-(arylmethylene)isoindolin-1-ones can be efficiently synthesized from various ynamides and boronic acids by palladium-catalyzed Heck–Suzuki–Miyaura domino reactions. This methodology has been applied to the total synthesis of lennoxamine and a concise route to this isoindolobenzazepine alkaloid was achieved in eight steps from 2,3-dimethoxybenzoic acid via a key intermediate ynamide.

1. Introduction

Substituted 3-methyleneisoindolin-1-ones of type **A**, and in particular those in which R^3 is an aromatic substituent (R^3 = Ar), are encountered in a number of naturally occurring products such as enterocarpam II, a member of the aristolactam alkaloids family[1] or the secophthalide–isoquinoline ene-lactam fumaridine[2] (Fig. 1).

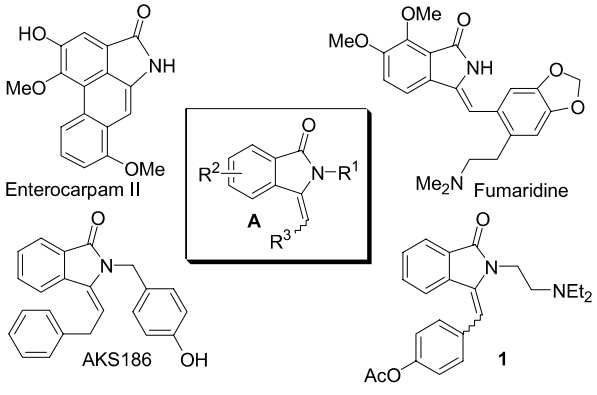

Figure 1. Naturally occurring and/or biologically active substituted 3-methyleneisoindolin-1-ones.

Isoindolin-1-ones of type **A** are also found as the structural feature of biologically active compounds such as AKS186 that displays vasorelaxant properties[3] or compound **1** whose hydrochloride was claimed to exhibit local anesthetic activity superior to that of procaine[4] (Fig. 1).

The synthesis of isoindolin-1-ones of type **A** has elicited considerable synthetic interest as several representative general strategies have been developed (Scheme 1). In the earliest routes [routes (a), Scheme 1], phthalimides of type **B** were often considered as starting materials and were converted to isoindolin-1-ones of type **A** by Wittig reaction with stabilized phosphoranes[5] or addition of organometallic reagents followed by dehydration of the resulting 3-hydroxyphthalimidines.[3,6] However, this approach can lead to a mixture of regioisomers in the case of an unsymmetrical substrate.[3,6] Furthermore, the synthesis of 3-(arylmethylene)-isoindolin-1-ones of type **A** where R^3 = Ar by the latter route requires the use of benzylic Grignard reagents as nucleophiles whose preparation is not always trivial. More recently, an interesting alternative benzylation procedure of phthalimides of type **B**, based on the photodecarboxylation of arylacetates, has been developed.[7] Phthalides of type **C** (or the corresponding open-chain keto-benzoic acids) are also useful precursors since they can be readily converted to compounds of type **A** by treatment with primary amines, followed by dehydration [route (b), Scheme 1].[8] Another general route towards substituted 3-methyleneisoindolin-1-ones of type **A** relies on an ortholithiation–anionic cyclization sequence initiated by treatment of *N*-acyl-2-bromobenzamides of type **D** with

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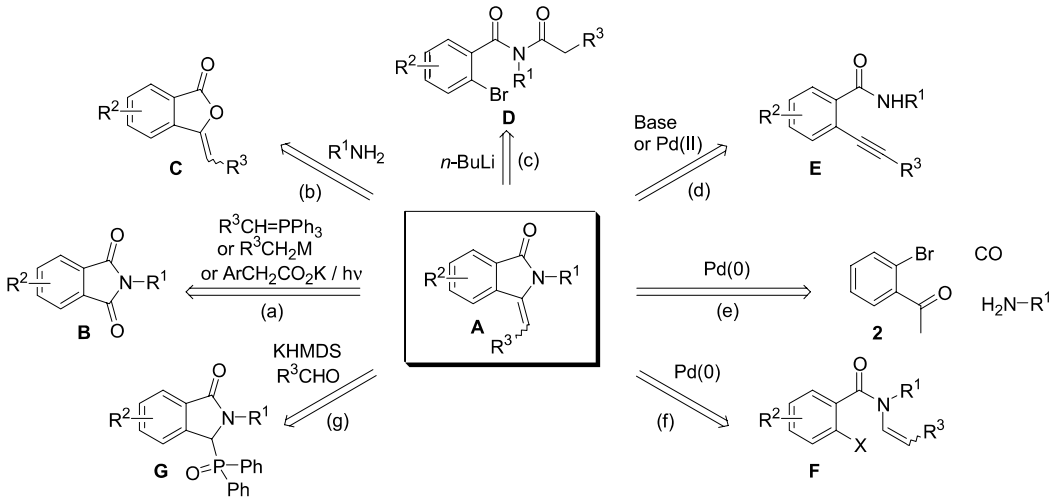
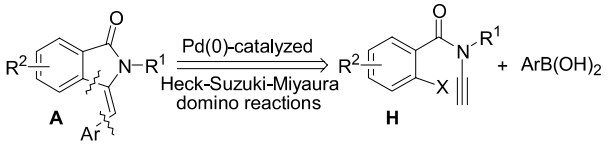


Scheme 1. Representative synthetic strategies towards substituted 3-methyleneisoindolin-1-ones of type **A**.

n-butyllithium, followed by dehydration of the resulting 3-hydroxyphthalimidines [route (c), Scheme 1].[9] Efficient syntheses of isoindolin-1-ones of type **A** have also been achieved by cyclization of 2-alkynylbenzamides of type **E** induced by treatment with a base or a palladium(II) catalyst [route (d), Scheme 1].[10,11] Interestingly, the disubstituted alkynes of type **E** are readily available by Sonogashira cross-coupling reactions involving 2-halobenzamides as substrates and, in some cases, both transformations leading to isoindolin-1-ones of type **A** have been carried out in a one-pot sequence.[10c] A palladium(0)-catalyzed three-component reaction involving 2-bromoacetophenone **2** and a variety of primary amines under carbon monoxide pressure can also be used to synthesize 3-methyleneisoindolin-1-ones of type **A** ($R^3=H$) [route (e), Scheme 1].[12] A related process has been described from 2-bromoaryl ketones wherein a titanium–isocyanate complex was used as the nitrogen donor.[13] Alternative palladium(0)-catalyzed processes towards compounds of type **A** exploit the synthetic potential of intramolecular Heck reactions of enamide derivatives of type **F** [route (f), Scheme 1].[14] Finally, the Horner condensation of 3-(diphenylphosphinoyl)isoindolin-1-ones of type **G** with a variety of aldehydes constitutes a particularly interesting entry to isoindolin-1-ones of type **A** that has culminated with several applications to natural products synthesis [route (g), Scheme 1].[15] Besides these main representative strategies, other reactions leading to isoindolin-1-ones of type **A** have also been reported.[16]

In recent years, the synthetic application of ynamides has expanded enormously.[17] Indeed, these stable electron-deficient variants of ynamines can participate in several transformations usually carried out with alkynes such as thermal, metal- or Lewis acid-catalyzed cycloadditions,[18–21] platinum(II)-catalyzed cycloisomerization,[22] ring-closing metathesis,[23] titanium(II)-mediated coupling reactions,[24] carbocupration,[25] hydroboration[26] and hydrohalogenation[27] followed by cross-coupling reactions, as well as sigmatropic rearrangements.[28] Some radical cyclization cascades involving ynamides as substrates have also been reported as a route to various nitrogen heterocycles, including substituted isoindolin-1-ones of type **A**.[29]

We became interested in the development of an alternative synthetic strategy towards a variety of (*E*)-3-(arylmethylene)isoindolin-1-ones of type **A** that proceeds from ynamides of type **H** and arylboronic acids and relies on Pd(0)-catalyzed Heck–Suzuki–Miyaura domino reactions (Scheme 2).



Scheme 2. Synthesis of 3-(arylmethylene)isoindolin-1-ones of type **A** by Heck–Suzuki–Miyaura domino reactions from ynamides of type **H**.

When we began our investigations on this project, hydrostannation[30] and an heteroannulation strategy towards 2-aminoindoles, based on the nucleophilic addition of amines to the triple bond of ynamides activated by an intramolecular arylpalladium(II) complex,[31] were the only reported examples of palladium-catalyzed processes involving ynamides as substrates. Herein, we report a full account of our work on the synthesis of 3-(arylmethylene)-isoindoloin-1-ones by Heck–Suzuki–Miyaura domino reactions involving ynamides,[32] as well as its application to the total synthesis of the natural product lennoxamine.

2. Results and discussion

In order to investigate the feasibility of the Pd(0)-catalyzed Heck–Suzuki–Miyaura domino reactions as a route to isoindolinones of type **A**, several ynamides of type **H** were prepared from 2-iodobenzoic acid **3**. This carboxylic acid was coupled with benzylamine, 2-bromobenzylamine and allylamine *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), cat. DMAP, CH_2Cl_2 or CH_2Cl_2/THF, rt] to afford the corresponding 2-iodobenzamides **4a** (60%), **4b** (81%) and **4c** (73%), respectively. After formation of the potassium amides (KHMDS, toluene, 0 °C to rt) and addition of the alkynyliodonium salt **5**,[33] the trimethylsilyl-substituted ynamides **6a** (48%), **6b** (72%) and **6c** (63%) were obtained in acceptable yields.[18a] Subsequent