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A short synthesis of lennoxamine via ynamides

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Abstract—Lennoxamine was synthesized in eight steps from 2,3-dimethoxybenzoic acid via an intermediate ynamide by using palladium-catalyzed Heck–Suzuki–Miyaura domino reactions.

Polycyclic nitrogen containing heterocycles are encountered in naturally occurring alkaloids and numerous physiologically active drugs.[1] Lennoxamine, an isoindolobenzazepine alkaloid, belongs to the *aporhoedane* series and was extracted from the Chilean plant *Berberis darwinii* (Fig. 1).[2] Although this compound has no important biological activity, its unique structural feature, five- and seven-membered rings fused with an aromatic moiety, has rendered this molecule attractive as a synthetically challenging target. Several total syntheses of lennoxamine have been reported relying on the construction of ring B or/and ring C as the key steps.[3]

Recently, we have shown that 3-(arylmethylene)isoindolin-1-ones of type **B** could be obtained from ynamides of type **A** by using palladium-catalyzed Heck–Suzuki–Miyaura domino reactions in the presence of an arylboronic acid (Scheme 1).[4]

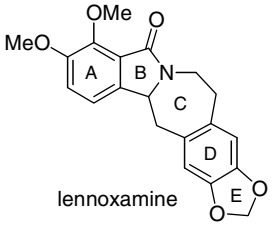
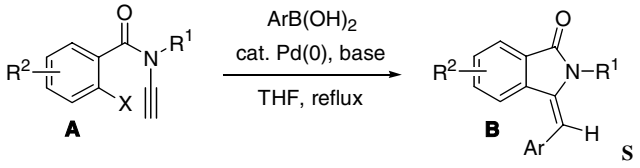
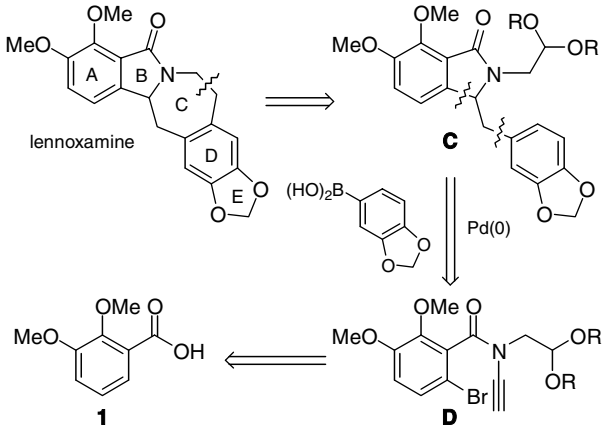


Figure 1. Structure of lennoxamine.



Scheme 1. Synthesis of 3-(arylmethylene)isoindolin-1-ones by Heck–Suzuki–Miyaura domino reactions.

As lennoxamine can arise from the cyclization of an isoindolinone of type **C** under acidic conditions followed by catalytic hydrogenation,[3i,p] it was envisaged to apply the Heck–Suzuki–Miyaura reactions to an ynamide of type **D**. The latter compound should be prepared from 2,3-dimethoxybenzoic acid **1** (Scheme 2).



Scheme 2. Retrosynthetic analysis of lennoxamine.

Keywords: Lennoxamine; Isoindolinones; Isoindolobenzazepines; Suzuki–Miyaura coupling; Palladium-catalyzed reactions.
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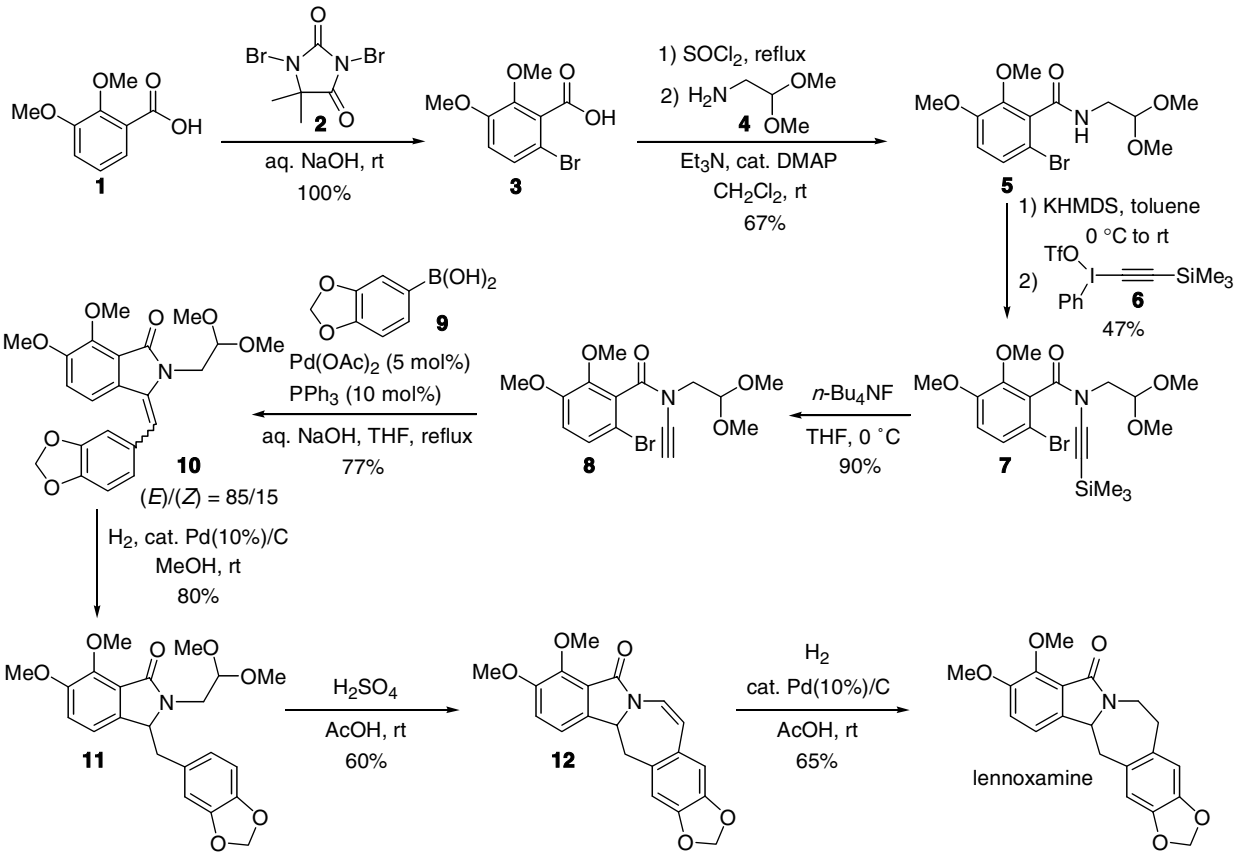

Scheme 3. Synthesis of lennoxamine.

The synthesis of lennoxamine (Scheme 3) began with the bromination of 2,3-dimethoxybenzoic acid **1** with 1,3-dibromo-5,5-dimethylhydantoin **2** (aqueous NaOH, rt),[5] which led to 2,3-dimethoxy-6-bromobenzoic acid **3** in quantitative yield. Carboxylic acid **3** was converted to the corresponding acyl chloride ($SOCl_2$, reflux) and the latter was coupled with aminoacetaldehyde dimethyl acetal **4** (Et_3N, cat. DMAP, CH_2Cl_2, rt) to afford the secondary amide **5** in 67% overall yield (one-pot process). After the formation of the potassium amide (KHMDS, toluene, 0 °C to rt) and condensation with the alkynyliodonium salt **6**,[6] ynamide **7** was obtained in modest yield (47%). Alternative alkynylation procedures did not provide satisfactory results in the case of amide **5**.[7] The trimethylsilyl group was then removed by treatment of **7** with tetrabutylammonium fluoride in THF to afford the terminal ynamide **8** (90%). The next task, that constitutes the key step of our synthetic plan, was to construct ring B and hence elaborate the isoindolone core of lennoxamine by the palladium-catalyzed Heck–Suzuki–Miyaura domino reactions.[4] Thus, the terminal ynamide **8** was treated with a catalytic amount of $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %) and a base (aqueous NaOH) in the presence of the commercially available boronic acid **9** that incorporates both the D and E rings of the natural product (THF, reflux). Under these conditions, the Heck–Suzuki–Miyaura domino reactions proceeded smoothly and the resulting 3-(arylmethylene)isoindolin-1-one **10** was isolated in 77% yield but as a mixture of two geometric isomers [$(E):(Z) = 85:15$].[8,9] The latter result was in sharp contrast with our initial observation that 3-(arylmethylene)isoindolin-1-ones of type **B** were obtained with high (*E*) stereoselectivity by Heck–Suzuki–Miyaura domino reactions from ynamides of type **A**.[4] Carbopalladations of alkynes are known to involve a *syn*-addition process but isomerization of the initially formed σ-vinylpalladium complex has been observed in some cases, presumably through a zwiterrionic palladium–carbene complex.[10] Although such a scenario cannot be ruled out in the carbopalladation of the triple bond of ynamide **8**, the particular structure of 3-(arylmethylene)isoindolin-1-one **10**, which possesses a rather electron-rich enamide moiety, may be responsible for the observed isomerization. The latter could occur through a reversible protonation of the double bond or a hydration–dehydration pathway.[11–13] A photochemical process could also be involved due to the light sensitivity of compound **10**.

However, this lack of stereoselectivity in the synthesis of compound **10** had no consequence for the total synthesis of lennoxamine since the mixture of geometric isomers was subsequently subjected to a catalytic hydrogenation (cat. Pd (10%)/C, 1 atm H_2, MeOH, rt) that led to 3-(arylmethyl)isoindolin-1-one **11** in 60% yield. Completion of the total synthesis could be achieved from compound **11**, as previously reported,[3i,3p] by treatment under acidic conditions (H_2SO_4 in AcOH, rt) that served to elaborate the seven-membered ring (ring C)[3i] and the

resulting dehydrolennoxamine **12** (60%) was finally hydrogenated (cat. Pd (10%)/C, 1 atm H_2, AcOH, rt) to afford lennoxamine in 65% yield (Scheme 3). The spectroscopic and analytical data of this compound were in perfect agreement with those reported in the literature.[3]

A concise route to lennoxamine has been developed from 2,3-dimethoxybenzoic acid (8 steps, 7% overall yield) using a strategy complementary to the previously reported approaches for the construction of the isoindolone core of this isoindolobenzazepine alkaloid, that relies on palladium-catalyzed Heck–Suzuki–Miyaura domino reactions from an intermediate ynamide.

Acknowledgements

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8. The ratio of the two geometric isomers was determined by ^{1}H NMR and their configuration was readily assigned by comparison with the data reported for the (*E*)-isomer.[3i] It was checked that purification of compound **10** by chromatography on silica gel did not lead to any isomerization since the crude product was already an 85/15 isomeric mixture.
9. As alkynylsilanes are known to be deprotected under alkaline conditions, the preparation of **10** could also be directly achieved from trimethylsilylynamide **7** by initial treatment with the base (aq NaOH, THF, reflux) followed by addition of the palladium catalyst and arylboronic acid **9** although the overall yield of compound **10** was not improved by this one-pot procedure.
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12. Protonation of the double bond in 3-(arylmethylene)-isoindolin-1-ones generates *N*-acyliminum cations that can be trapped by a nucleophile, including water, to generate the corresponding *N*-acylcarbinolamines. For some applications, see: (a) Chihab-Eddine, A.; Daïch, A.; Jilale, A.; Decroix, B. *Heterocycles* **2002**, *58*, 449–456; (b) Daïch, A.; Marchalin, S.; Pigeon, P.; Decroix, B. *Tetrahedron Lett.* **1998**, *39*, 9187–9190.
13. Grignard additions to phthalimides followed by dehydration of the resulting *N*-acylcarbinolamines is a well-known route towards 3-(arylmethylene)isoindolin-1-ones, see for example: Kato, Y.; Ebiike, H.; Achiwa, K.; Ashizawa, N.; Kurihara, T.; Kobayashi, F. *Chem. Pharm. Bull.* **1990**, *38*, 2060–2062.