SYNTHESIS OF LENNOXAMINE *via* THE INTRAMOLECULAR CYCLIZATION OF ALKYNYLAMIDE

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This paper presents the formal synthesis of lennoxamine (**1**), the key step [**4** into **10** *via* **9**] of which is a novel palladium-catalyzed coupling reaction followed by intramolecular cyclization of alkynylamide.

KEY WORDS lennoxamine; lactam synthesis; alkynylamide; palladium catalyst; coupling reaction

Lennoxamine (**1**),[1] a minor alkaloid obtained in racemic form from *Berberis darwinii* Hook (*Berberidaceae*) in 1984, has a rare isoindolo[1,2-*b*][3]benzazepine ring system. Three interesting syntheses of **1** have been reported, two of which (Brossi[2], Moody[3]) are based on the cyclization of arylbenzazepine derivatives **2** and one (Napolitano[4]) on the cyclization of benzylisoindolone **3**.[5]

This paper presents the synthesis of the key intermediate **3**, *i.e.*, the formal synthesis of lennoxamine (**1**), *via* the novel arylation and intramolecular cyclization of the *o*-ethynylbenzamide derivative **4**.

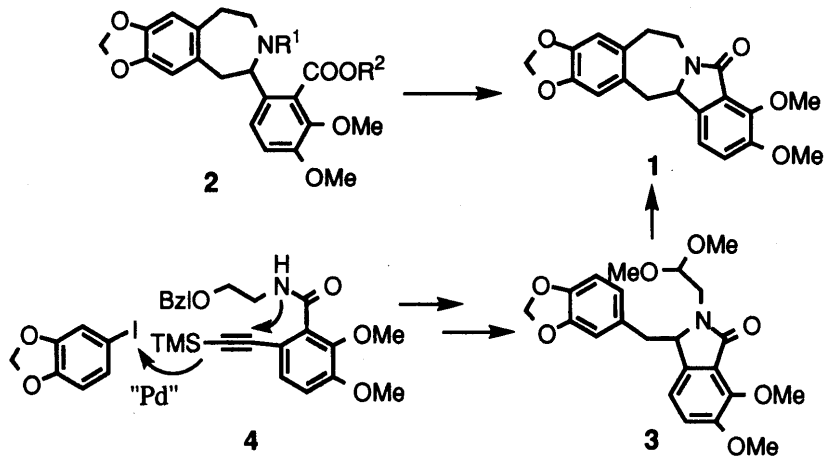

Chart 1

The synthesis of **3** is shown by Charts 1 and 2. In this research the key step is the intramolecular cyclization of alkynylamides into alkylidenelactams.[6,7] Alkylidenelactam (such as **10**) formation by the 5-*exo*-*dig*-cyclization of alkynylamides (such as *o*-ethynylbenzamides **4** and **9**) has been carefully examined by the authors and effective means for the synthesis of isoindolones have been established.[8]

The synthesis of **3** was achieved in nine or ten steps from lactone **5**[9] as shown in Chart 2. Alkynylamide **4** could be easily synthesized in good yield as follows: a) reduction of **5** with zinc in AcOH-THF,[10] b) condensation of carboxylic acid **6** with 2-(benzyloxy)ethylamine, c) protection of the amide group of **7** with Meerwein reagent, d) preparation of trimethylsilylacetylene **8** and e) reconversion of imidate **8** to amide **4**. Treatment of **7** with strong bases (n-BuLi, LHMDS) in THF afforded chloromethylideneisoindolones in quantitative yields, with **12** as the major stereoisomer.[11] The arylation of **12** to **10** was initially attempted, but without success. Also,

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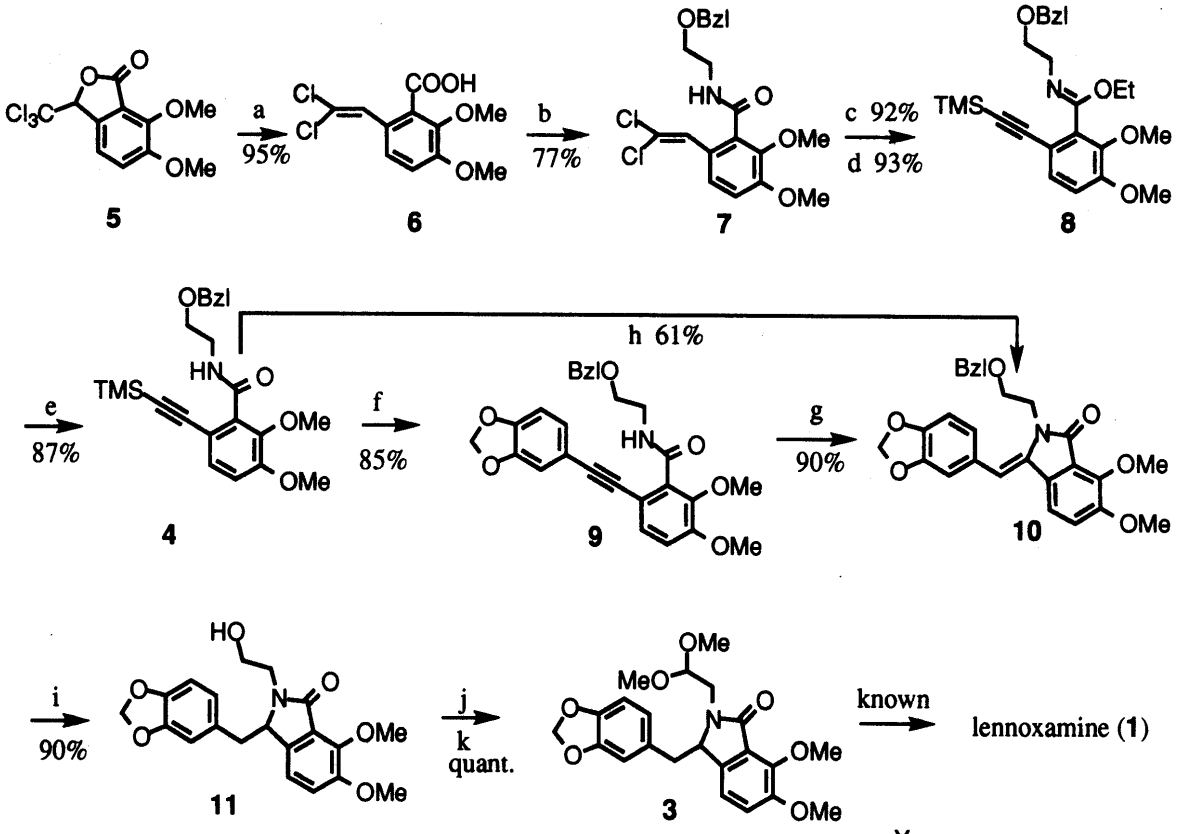
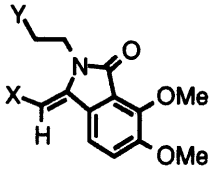
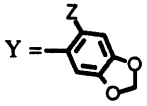


Chart 2

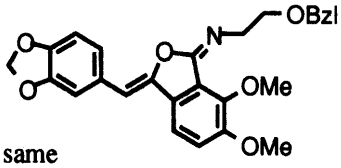
Reagents and Conditions: a) Zn, AcOH-THF = 8 : 5, 60°C, 2h; b) $BzlOCH_2CH_2NH_2$, DEPC, Et_3N, CH_2Cl_2, r.t., 5h; c) $Et_3O^+BF_4^-$, CH_2Cl_2, 0→60°C, 10h; d) n-BuLi (2.1 eq.), Et_2O, -10°C, 1h, then, TMSCl, -50→0°C, 1h; e) TMSCl (1.2 eq.), NaI (1.2 eq.), MeCN, 0°C→r.t., 12h; f) $Pd(OAc)_2$ (0.05 eq.), PPh_3 (0.2 eq.), Ag_2CO_3 (1 eq.), Et_3N (3 eq.), ArI (1.3 eq.), Bu_4NCl (1 eq.), THF, r.t., 3h; g) LHMDS (1 eq.), THF, 0°C→r.t., 1h; h) After the reaction of step f, LHMDS (2 eq.), r.t., 1h; i) 10%Pd-C, H_2 (3 atm), THF-MeOH-AcOH = 1 : 1 : 0.5, r.t., 36h; j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78→0°C; k) *p*-TsOH (cat.), $CH(OMe)_3$ (1.2 eq.), MeOH, reflux.



12 : X = Cl, Y = OBzl
13 : X = Cl, I, TMS



Z = H, Br, I,



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various *N*-(2-arylethyl)methylideneisoindolone derivatives **13** were prepared by the same method but, in all cases, attempts to use them for obtaining the lennoxamine skeleton were unsuccessful.

The general palladium-mediated coupling reaction (Sonogashira reaction)[12] of alkynylamides (**8** and **4** without the TMS-protecting group) with aryl iodides was carried out, but the desired **9** could hardly be obtained. **9** was finally obtained in high yield by reaction of **4** with aryl iodide under the conditions for step f in Chart 2. It should be pointed out that TMS-acetylene coupled with aryl iodide at the position of the TMS group.[13] The addition of silver carbonate (1 eq.) promoted this reaction with subsequently better yield. Although the role of silver ions is not clear, silver acetylide formation may occur at the initial step.[14] The cyclization of **9** using one molar equivalent of LHMDS in THF at room temperature afforded **10** in 90% yield along with imidate **14**[15] in 3% yield. One-pot reaction of **4** to **10** *via* **9** was carried out. Successive addition of LHMDS (2 eq.) in the same vessel after step f gave

10 in 61% yield. The higher reaction temperature (60°C) at step f in Chart 2 afforded a mixture of **10** and **14** (ratio 1 : 1) in 76% yield. But this should not be taken to mean that the palladium-catalyzed cyclization of alkynylamide **9** occurred, since **9** was confirmed to be converted to **10** without palladium as in step f in Chart 2.

The catalytic reduction of **10** gave alcohol **11**, followed by Swern oxidation to afford the unstable aldehyde, which was immediately converted to dimethyl acetal **3**. The spectral data (^{1}H-NMR, IR and mass) of **3** showed complete agreement with those of an authentic sample reported in the literature.[4] Napolitano[4] has reported the conversion of **3** to **1**; in the present study, authors achieved formal synthesis of lennoxamine (**1**).

In summary, a new-type coupling reaction of TMS-acetylene with aryl iodide, the convenient intramolecular cyclization of alkynylamides to lactams, and their application to the synthesis of lennoxamine (**1**) are presented.

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6) After completion of the present work, reports on the cyclization of alkynylamides by n-Bu_4NF or $LiAl(NHBn)_4$ to methylidenepyrrolidinones have appeared: Jacobi P. A., Brielmann H. L., Hauck S. I., *Tetrahedron Lett.*, **36**, 1193-1196 (1995); Jacobi P. A., Guo J., *Tetrahedron Lett.*, **36**, 2717-2720 (1995).
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8) Detailed results for the synthesis of other lactams will appear in a full paper.
9) Lactone **5** was prepared in 87% yield by reaction of 2,3-dimethoxybenzoic acid with chloral hydrate according to Desai H. K., Usgaonkar R. N., *J. Indian Chem. Soc.*, **40**, 239-240 (1963). All new compounds were fully characterized by ^{1}H-NMR, IR, and mass spectrometry and elemental analysis (C,H,N) or exact masses.
10) A mixture of AcOH and THF increased the yield of **6**. Reference 9 specifies the formation of (β,β-dichloroethyl)benzoic acid derivatives under the same conditions.
11) Stereochemistry of **10**, **12**, **13** and **14** was confirmed by NOE of olefinic protons with the aromatic protons at the *ortho*-position.
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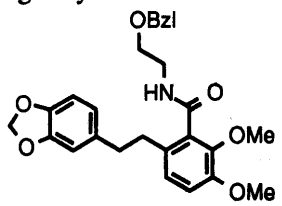
15) Catalytic hydrogenation under the neutral condition and hydrolysis of **14** gave amide **15** and lactone **16**, respectively, each in good yield.



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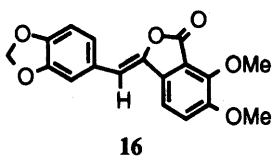

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