Pergamon

Tetrahedron Letters, Vol. 36, No. 37, pp. 6733-6734, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01364-4

Sulfur-Directed 5-*Exo* Selective Aryl Radical Cyclization onto Enamide: A Simple Route to Chilenine

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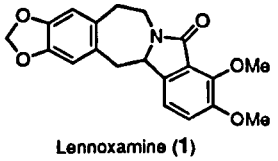
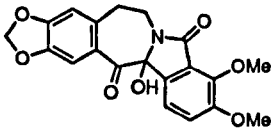
Abstract: Bu_3SnH-mediated aryl radical cyclization of the *N*-(*o*-bromoaroyl)enamine **5** took place in a 5-*exo-trig* manner exclusively to give isoindolone **7**, which was transformed into the key intermediate **11** for the synthesis of isoindolobenzazepine alkaloid chilenine (**2**).

Lennoxamine (**1**)[1] and chilenine (**2**)[2] (both racemates) are the first examples of a new class of isoindolobenzazepine alkaloids isolated from the Chilean barberries *Berberis darwinii* Hook and *Berberis empetrifolia* Lam, respectively. While these alkaloids do not appear to possess any useful pharmacological activities, their unique structural feature renders these molecules attractive synthetic targets.[3-5] Herein we report a simple route to chilenine using sulfur-directed regioselective aryl radical cyclization onto an enamide as a key step.



Lennoxamine (**1**)

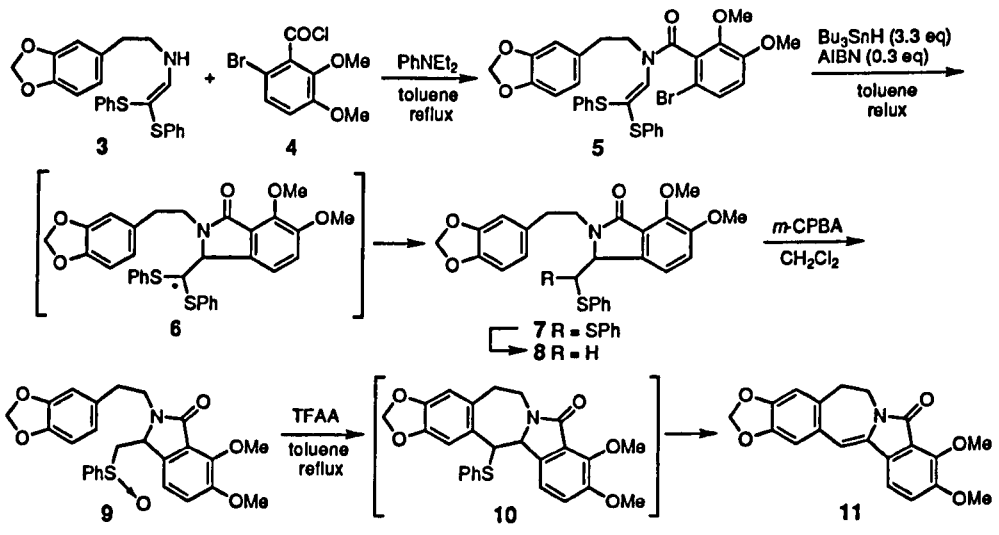


Chilenine (**2**)

The radical precursor **5** was easily prepared by condensation of 2-(3,4-methylenedioxyphenyl)ethylamine with bis(phenylthio)acetaldehyde, followed by *N*-acylation of the resulting enamine **3** [δ 3.27 (q, 2 H, J = 6.5 Hz, NCH_2), 4.8-5.3 (br, 1 H, NH)] with 6-bromo-2,3-dimethoxybenzoyl chloride **4**[6] (58% overall yield). The compound **5** was then subjected to the usual radical cyclization conditions (Bu_3SnH and a catalytic quantity of AIBN in boiling toluene). The rate of generation of the aryl radical from **5** was rather slow, and hence a concomitant partial desulfurization of the cyclization product **7** to the mono(phenylthio) compound **8** was unavoidable. However, we envisioned that the compound **8** would be a more suitable intermediate for the synthesis of target molecules. Therefore, the bromide **5** was treated with 1.1 equiv of Bu_3SnH and then further with 2.2 equiv of Bu_3SnH (total 3.3 equiv) *in situ* to give **8** as a sole product in 66% yield.

The formation of the initial cyclization product **7** from the bromide **5** may be due largely to the high stability of the intermediate, the sulfur-substituted radical **6**, which was generated by a 5-*exo* aryl radical cyclization onto the enamide. This result is of great interest in view of the previous works[7] on the aryl radical

cyclization of other related enamides, which usually take place in a 6-*endo* mode to give tetrahydroisoquinoline derivatives through the intermediates of the highly stable acylamino radicals.



Oxidation of **8** with *m*-CPBA gave the sulfoxide **9**, which was then treated with trifluoroacetic anhydride in boiling toluene to give the tetracyclic compound **11** in 69% yield. The formation of **11** from **9** may involve an intramolecular aromatic substitution of the Pummerer rearrangement intermediate to form **10**. This step is then followed by elimination of benzenethiol under the acidic conditions employed to give **11**. Since the compound **11** has previously been converted into chilenine (**2**) in one-pot (dimethyl dioxirane and then aq. $NaHCO_3$) by Danishefsky,[4] the whole sequence of the reactions herein described constitutes, in a formal sence, a total synthesis of chilenine.

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6. Compound **4** was readily prepared from 2,3-dimethoxybenzoic acid via bromination with 1,3-dibromo-5,5-dimethylhydantoin in NaOH solution (Auerbach, J.; Weissman, S.A.; Blacklock, T.J.; Angeles, M.R.; Hoogsteen, K. *Tetrahedron Lett.* **1993**, *34*, 931-934) followed by treatment with thionyl chloride.
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(*Received in Japan* 30 *June* 1995; *revised* 17 *July* 1995; *accepted* 20 *July* 1995)