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A Short Synthesis of Lennoxamine Using a Radical Cascade

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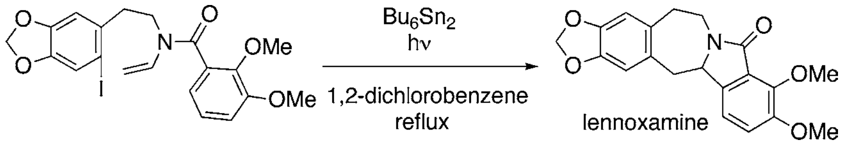
ABSTRACT



A short synthesis of lennoxamine has been achieved by using a radical cascade involving aryl radical-induced 7-*endo* cyclization and homolytic aromatic substitution.

Lennoxamine (**1**), an isoindolobenzazepine alkaloid, was isolated from Chilean *Berberis darwinii* (Figure 1).[1] Owing to its unique tetracyclic ring system, the alkaloid **1** has attracted much attention from synthetic chemists, and efforts have culminated in the total synthesis of **1**.[2]

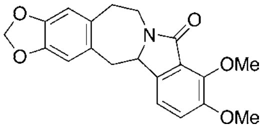
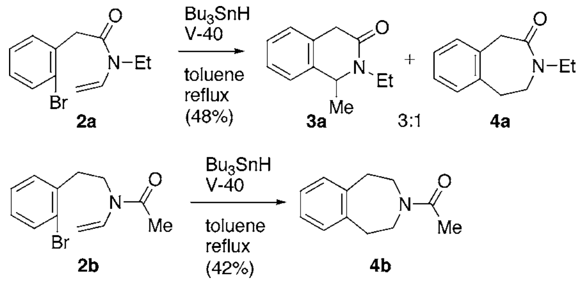


Figure 1. Structure of lennoxamine (**1**).

Scheme 1



We recently reported that regioselectivity of aryl radical cyclization onto enamides can be shifted by positional change of the carbonyl group.[3] For example, treatment of enamide **2a** with Bu_3SnH in the presence of 1,1′-azobis(cyclohexanecarbonitrile) (V-40) in boiling toluene causes aryl radical cyclization to give 6-*exo* cyclization product **3a** along with a small amount of 7-*endo* cyclization product **4a**, whereas enamide **2b** undergoes 7-*endo* aryl radical cyclization to afford benzazepine **4b** exclusively (Scheme 1).[3b] As an application of the latter process, we envisioned the synthesis of lennoxamine (**1**) using a radical cascade involving 7-*endo*

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[1] Natural **1** was isolated as a racemate, see: Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett.* **1984**, *25*, 599.

[2] Quite recently (+)-**1** was synthesized, see: (a) Comins, D. L.; Schilling, S.; Zhang, Y. *Org. Lett.* **2005**, *7*, 95. For the recent syntheses of racemic **1**, see: (b) Sahakitpichan, P.; Ruchirawat, S. *Tetrahedron* **2004**, *60*, 4169. (c) Kim, G.; Kim, J. H.; Kim, W.-J.; Kim, Y. A. *Tetrahedron Lett.* **2003**, *44*, 8207. (d) Koseki, Y.; Katsura, S.; Kusano, S.; Sakata, H.; Sato, H.; Monzene, Y.; Nagasaka, T. *Heterocycles* **2003**, *59*, 527. (e) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923. (f) Ruchirawat, S.; Sahakitpichan, P. *Tetrahedron Lett.* **2000**, *41*, 8007. (g) Couture, A.; Deniau, E.; Grandclaudon, P. Hoarau, C. *Tetrahedron* **2000**, *56*, 1491. (h) Koseki, Y.; Kusano, S.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett.* **1999**, *40*, 2169. (i) Ishibashi, H.; Kawanami, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 817.

[3] (a) Ishibashi, H.; Kato, I.; Takeda, Y.; Kogure, M.; Tamura, O. *Chem. Commun.* **2000**, 1527. (b) Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibasi, H. *J. Org. Chem.* **2005**, *70*, 1922. See also: (c) Kamimura, A.; Taguchi, Y.; Omata, Y.; Hagihara, M. *J. Org. Chem.* **2003**, *68*, 4996.

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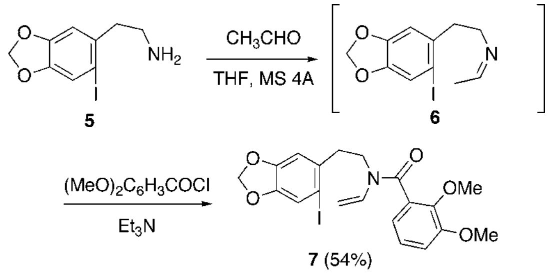
aryl radical cyclization and homolytic aromatic substitution (Scheme 3).[4,5] We report herein a concise synthesis of **1** according to this strategy.

Our investigation began with preparation of enamide **7** (Scheme 2). Amine **5**[6] was treated with acetaldehyde in THF in the presence of molecular sieves 4A at 10 °C[7] to give imine **6**, which was then treated with 2,3-dimethoxybenzoyl chloride in the presence of triethylamine to afford enamide **7** in 54% yield from **5**.

Scheme 2



When enamide **7** was treated with Bu_3SnH (1.5 equiv) in the presence of V-40 (2.0 equiv) in boiling toluene using a slow addition technique, lennoxamine **(1)** (mp 227−228 °C, lit.[2b] mp 226−227 °C) and 7-*endo* cyclization product **9** were obtained in 16 and 32% yields, respectively (Scheme 3) (Table 1, entry 1). Formation of **1** may involve 7-*endo* cyclization of the aryl radical generated from **7** followed by homolytic aromatic substitution of the resulting α-amidoyl radical **8** onto the dimethoxyphenyl group.[8] Formation of **9** might be due to the reduction of α-amidoyl radical **8** with Bu_3SnH.

Scheme 3

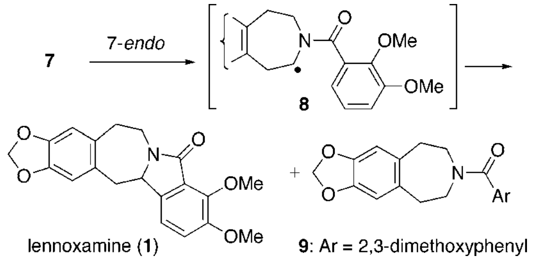


Table 1. Radical Reaction of Enamide **7**

entry	conditions (equiv)[a]	yield[b] (%) **1**	yield[b] (%) **9**
1	Bu_3SnH (1.5), V-40 (2.0), toluene	16	32
2	Bu_6Sn_2 (2.0), *hν*, toluene	18	0
3	Bu_6Sn_2 (2.0), *hν*, chlorobenzene	25	0
4	Bu_6Sn_2 (2.0), V-40 (2.0), *hν*, chlorobenzene	26	0
5	Bu_6Sn_2 (2.0), *hν*, 1,2-dichlorobenzene	40	0
6	Me_6Sn_2 (2.0), *hν*, 1,2-dichlorobenzene	41	0

[a] All reactions were carried out in refluxing solvent (7 mM). [b] Isolated yield.

The use of ditin instead of Bu_3SnH might prevent the formation of **9**, and several experiments were carried out to improve the yield of product **1** by using ditin under photochemical conditions.[9]

Irradiation of a mixture of **7** and Bu_6Sn_2 (2.0 equiv) with a sun lump in boiling toluene, as expected, gave no compound **9**, but only a 18% yield of the requisite lennoxamine (**1**) was obtained (entry 2). The dehalogenated product of **7** was also obtained in entry 2. We assumed that an abstraction of a benzylic hydrogen atom from toluene used as a solvent might occur, and chlorobenzene was therefore used as a solvent to give lennoxamine (**1**) in 25% yield (entry 3).

Recently, Beckwith et al. have suggested that the radical species generated from a radical initiator such as V-40 plays an important role in the hydrogen atom abstraction for the rearomatization of an intermediary cyclohexadienyl radicals.[5c] Hence, 2 equiv of V-40 were added, but no improvement in the yield of the product **1** was observed (entry 4).

Finally, a more satisfactory result was obtained by carrying out the reaction using high boiling 1,2-dichlorobenzene as a solvent. These conditions gave lennoxamine (**1**) in 40% yield (entry 5). Using Me_6Sn_2 instead of Bu_6Sn_2 gave a similar result (41%) (entry 6).

In conclusion, three-step synthesis of lennoxamine (**1**) from amine **5** has been achieved in 22% overall yield. The present synthesis of **1** clearly demonstrates the usefulness of the radical cascade process involving a homolytic aromatic substitution for the synthesis of nitrogen-containing polycyclic compounds.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **7**, **1**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[4] For reviews on radical cascades, see: (a) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2225. (b) *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215. For a radical cascade involving *endo*-selective aryl radical cyclization onto enamide, see: (c) Ishibashi, H.; Ishita, A.; Tamura, O. *Tetrahedron Lett.* **2002**, *43*, 473. See also, ref 3b.

[5] For recent references on homolytic aromatic substitution, see: (a) Ohno, H.; Iwasaki, H.; Eguchi, T.; Tanaka, T. *Chem. Commun.* **2004**, 2228. (b) Bennasar, M.-L.; Roca, T.; Ferrando, F. *Tetrahedron Lett.* **2004**, *45*, 5605. (c) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95 and references therein.

[6] Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264.

[7] García, A.; Rodríguez, D.; Castedo, L.; Saá, C.; Domínguez, D. *Tetrahedron Lett.* **2001**, *42*, 1903.

[8] For an example of radical addition of an α-amidoyl radical onto an aromatic ring, see: Gribble, G. W.; Fraser, H. L.; Badenock, J. C. *Chem. Commun.* **2001**, 805.

[9] For examples of homolytic aromatic substitution using irradiation of ditin with sunlamp, see: (a) Marion, F.; Courillion, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095. (b) Bennasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem.* **2001**, *66*, 7547. (c) Bowman, W. R.; Bridge, C. F.; Cloonan, M. O.; Leach, D. C. *Synlett* **2001**, 765. (d) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem. Eur. J.* **1998**, *4*, 67. See also ref 5b.