doi:10.1246/cl.2012.44
44 Published on the web December 24, 2011

Synthesis of 2-Iminoindolines via Samarium Diiodide Mediated Reductive Cyclization of Carbodiimides

Takayuki Ishida, Chihiro Tsukano, and Yoshiji Takemoto*
Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501

(Received October 17, 2011; CL-111019; E-mail: takemoto@pharm.kyoto-u.ac.jp)

A method of synthesizing 2-iminoindolines using samarium diiodide (SmI_2) is reported. In the presence of *tert*-butyl alcohol, treatment of carbodiimides bearing α,β-unsaturated carbonyl moieties with a stoichiometric amount of SmI_2 afforded 2-iminoindolines in moderate to high yields. The products were isolated after Boc protection of the amidine moieties. This reaction proved to be applicable to lactams and acyclic/cyclic esters as substrates.

Indole/indoline skeletons are one of the fundamental structural units frequently observed in natural products and pharmacologically active agents, so synthetic chemists continue to develop novel and efficient methods for synthesizing these privileged structures.[1] Among the broad range of such structures, 2-iminoindolines and 2-aminoindoles[2] are substructures found in natural alkaloids such as flustramine C and perophoramidine (Figure 1).[3,4] Diverse methods for the synthesis of these classes of compounds have been reported in the literature. Many of the reported methods adopted tether-dependent condensation of oxindole derivatives[5a–5d] or oxidative cyclization of indoles;[5e] synthetic routes based on various strategies, including aza-Pauson–Khand-type reactions,[6a] heteroannulation of *N*-alkynylanilines,[6b] ring enlargement of aminoazirines,[6c] addition of azides to indoles,[6d] oxidation of aminals,[6e] and amidination of aryl halides,[6f] have been introduced. Mild and selective synthetic methods for these substructures are still in high demand. In this communication, we disclose SmI_2-promoted intramolecular reductive cyclizations of carbodiimides possessing unsaturated carbonyl moieties, to provide 2-iminoindolines bearing quaternary-carbon centers at the C3 position.

The use of SmI_2 in synthetic chemistry has flourished since Kagan and his co-workers introduced it as a powerful one-electron reductant.[7] Its versatility in the construction of carbon–carbon bonds and its excellent functional group selectivity enable formation of numerous structurally complex skeletons found in natural products.[8] There have been many studies of its reductive homo-/heterocoupling reactions with electron-withdrawing groups.[9] To the best of our knowledge, however, no similar reactions involving carbodiimides have been reported in the literature.[10] Carbodiimides are well-established as precursors for the construction of amidines by reaction with a broad range of organometallic species,[11] but their applicability as radical acceptors has been regarded as rather limited.[12]

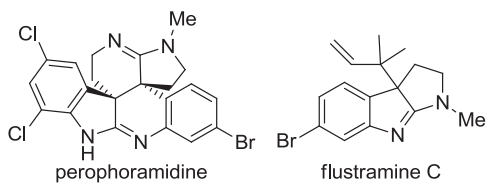
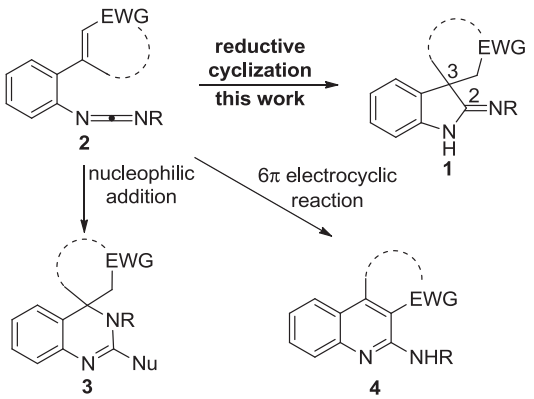


Figure 1. Natural products containing 2-iminoindoline/2-aminoindole skeletons.

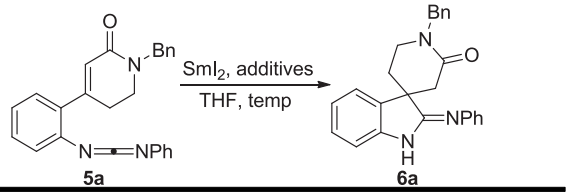
Recently, Wood et al. reported a synthesis of oxindoles by SmI_2-promoted intramolecular cyclization of aryl isocyanates possessing a cyclohexenone moiety, in the course of synthetic studies of welwitindolinone A isonitrile.[9g] Inspired by their results, we envisaged that the bond between a quaternary-carbon center and an imine carbon in iminoindoline **1** could be constructed by connecting different electron-withdrawing groups, i.e., an α,β-unsaturated carbonyl moiety and carbodiimide in **2** (Scheme 1). Radical or anionic species generated from unsaturated carbonyl groups using SmI_2 would attack the central carbons of carbodiimides, or vice versa. Although the syntheses of dihydroquinazoline **3** and 2-aminoquinoline **4** by tandem nucleophilic addition and 6π electrocyclic reaction of analogous substrates have been reported, respectively,[13,14] there are no similar examples of cyclization to construct quaternary-carbon centers. Thus, we started to seek mild conditions for the desired cyclization.

As a model substrate containing a partial perophoramidine structure for investigation of the reaction, we synthesized lactam derivative **5a**.[15] The results of optimization of the reaction conditions are shown in Table 1. Substrate **5a** was treated with SmI_2 in THF solution. No reaction occurred at −78 °C (Entry 1), but the desired reaction proceeded at ambient temperature to give the cyclized product **6a** as a single product (Entry 2). The use of additives improved the yields, and *tert*-butyl alcohol proved to be a better additive than HMPA[16] (Entries 3 and 4). Other additives such as LiCl[17a] and NiI_2[17b] showed no significant effect on the reaction (Entries 5 and 6). Product **6a** was converted to the Boc derivative **7a** as a single regioisomer in excellent yield; the structure was unambiguously determined by X-ray crystallography[18] (Scheme 2).



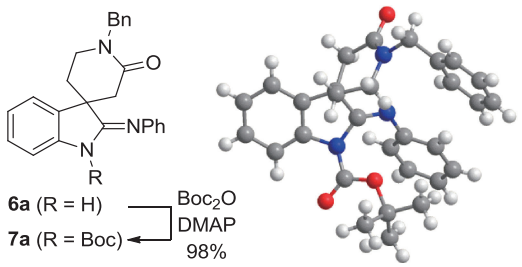
Scheme 1. Synthetic strategy.

Table 1. Optimization of reaction conditions



Entry[a]	Temp	Additives	Yield/%
1	−78 °C	none	N.R.
2	rt	none	55
3	rt	HMPA[b]	78
4	rt	*t*-BuOH[c]	83
5	rt	*t*-BuOH[c] + LiCl[d]	68
6	rt	*t*-BuOH[c] + NiI_2[e]	79

[a]Substrate solutions were added to 0.1 M SmI_2 solutions (2.4 equiv). [b]10 vol % in SmI_2 solution. [c]2.2 equiv. [d]10 equiv. [e]5 mol %.

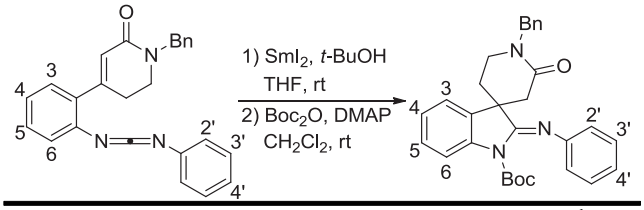


Scheme 2. Derivatization of **6a** and X-ray structure of **7a**.

Next, we investigated the scopes of the substrates for SmI_2-mediated reductive cyclizations (Table 2). Since some products were unstable, the cyclization yields were evaluated after treatment of the crude materials with Boc_2O and DMAP.[19] With regard to the substituents on the tethering aromatic rings, both electron-donating and chlorine functionalities, including a conformationally restricting substituent at the 3-position of the substrate, were tolerated, and products **7b**–**7e** were obtained in good to high yields (Entries 1–4). When substrates that possessed substituents on the other aromatic ring of the carbodiimides were examined, some unidentified by-products were obtained by reductive cyclization, resulting in moderate yields of the desired products (Entries 5–9). Interestingly, such decreases in the product yields seemed to be general, and independent of the properties of the substituents. Although it made little difference in the model study using substrate **5a**, a combination of inverse addition and modification of the of SmI_2, and increased amounts of *tert*-butyl alcohol (Table 2, condition B), proved to be effective in achieving complete conversion and obtaining the products in good to high yields. In the reaction with substrate **5f**, a small amount of product resulting from 6π electrocyclic reaction was detected, presumably as a result of Lewis acid promoted acceleration by a chelated Sm species.

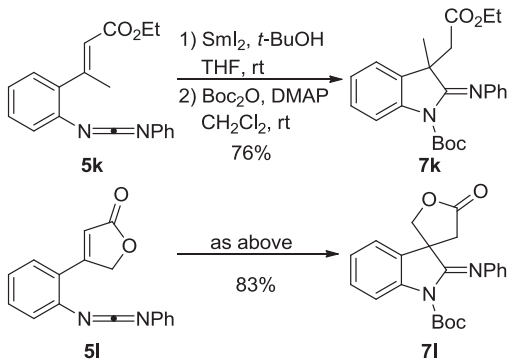
We also applied the reductive cyclization to esters (Scheme 3). The β,β-disubstituted carbonyl moieties proved to be essential, as shown by the fact that the reaction with the corresponding ethyl cinnamate resulted in a complex mixture in which dimerized or trimerized products were detected by mass

Table 2. Substrate scopes of reductive cyclization



Entry[a]	Substrate	Substituent	Product	Yield/% (A[b]/B[c])
1	**5b**	3-MeO	**7b**	75/—
2	**5c**	4-Me	**7c**	87/—
3	**5d**	4-MeO	**7d**	73/—
4	**5e**	4-Cl	**7e**	62/—
5	**5f**	2′-MeO	**7f**	42/66
6	**5g**	2′-Cl	**7g**	45/86
7	**5h**	3′-Me	**7h**	65/86
8	**5i**	4′-MeO	**7i**	46/74
9	**5j**	4′-F	**7j**	54/87

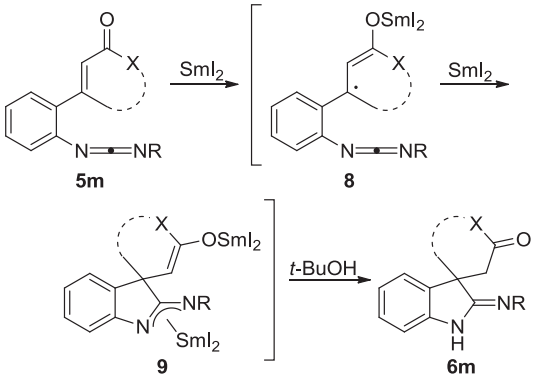
[a]All reactions were carried out on 0.100 mmol scale. [b]A indicates yield from condition A: THF solution of substrate and *t*-BuOH (2.2 equiv) were added to THF solution of SmI_2 (2.4 equiv). [c]B indicates yield from condition B: THF solution of SmI_2 (2.1–2.2 equiv) were added to THF solution of substrate and *t*-BuOH (10 equiv).



Scheme 3. Cyclization of acyclic/cyclic esters.

spectrometry. The acyclic substrate **5k** and lactone **5l** were examined and in both cases, the optimal reaction conditions (condition B in Table 2) gave the desired products in high yields. It is known that addition of HMPA was essential for the inter-/intramolecular homocoupling reactions of α,β-unsaturated esters,[9d] but in our case, only *tert*-butyl alcohol was required for these intramolecular reductive cyclization where one of α,β-unsaturated ester was replaced by a carbodiimide.

Scheme 4 shows a possible mechanism of reductive cyclization. First, the carbonyl oxygen of substrate **5m** coordinates to SmI_2, and reduction of the unsaturated carbonyl group results in a radical anionic species **8**. This radical attacks the carbon in the carbodiimide faster than the samarium enolate does, and further reduction by the second SmI_2 provides Sm amidinate **9**. As shown by the fact that the cyclized product was obtained in the absence of *tert*-butyl alcohol (Table 1, Entry 2), dianion **9** can be generated without the assistance of any proton source. Finally, protonation of **9** gave reductively cyclized iminoindo-



Scheme 4. Possible mechanism.

line **6m**. It is still unclear whether the formation of carbon–carbon bonds is promoted by chelation between a carbodiimide moiety and SmI_2 prior to cyclization. The reported instability and difficulty in generation of nitrogen-centered radical species[12] might suggest direct generation of the dianion **9** from the chelated complex.

In summary, we have developed a synthetic method for producing (spiro)-2-iminoindolines via SmI_2-mediated reductive cyclization of carbodiimides bearing unsaturated carbonyl moieties such as lactams and acyclic/cyclic esters. This reaction afforded various 2-iminoindolines in good to high yields. To the best of our knowledge, this is the first example of a pinacol-type coupling reaction, promoted by SmI_2, using carbodiimide functionalities.

This work was supported in part by a Grant-in-Aid for Scientific Research (B) and "Targeted Proteins Research Program" from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Y.T.).

References and Notes

1 For a recent review on indole synthesis, see: G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.

2 It was reported these two classes of compounds are in equilibrium with each other, see: a) A. Deberly, J. Bourdais, *Tetrahedron Lett.* **1971**, *12*, 3049. b) R. E. Harmon, G. Wellman, S. K. Gupta, *J. Heterocycl. Chem.* **1972**, *9*, 1191.

3 a) J. S. Carlé, C. Christophersen, *J. Org. Chem.* **1981**, *46*, 3440. b) T. Kawasaki, R. Terashima, K.-e. Sakaguchi, H. Sekiguchi, M. Sakamoto, *Tetrahedron Lett.* **1996**, *37*, 7525.

4 a) S. M. Verbitski, C. L. Mayne, R. A. Davis, G. P. Concepcion, C. M. Ireland, *J. Org. Chem.* **2002**, *67*, 7124. b) J. R. Fuchs, R. L. Funk, *J. Am. Chem. Soc.* **2004**, *126*, 5068.

5 a) See ref. 3b. b) Y. Jiang, J. Zhao, L. Hu, *Tetrahedron Lett.* **2002**, *43*, 4589. c) Y. A. O. Barbosa, D. J. Hart, N. A. Magomedov, *Tetrahedron* **2006**, *62*, 8748. d) A. Sabahi, A. Novikov, J. D. Rainier, *Angew. Chem., Int. Ed.* **2006**, *45*, 4317. e) M. Ohno, T. F. Spande, B. Witkop, *J. Am. Chem. Soc.* **1968**, *90*, 6521.

6 a) D. Aburano, T. Yoshida, N. Miyakoshi, C. Mukai, *J. Org. Chem.* **2007**, *72*, 6878. b) B. Witulski, C. Alayrac, L. Tevzadze-Saeftel, *Angew. Chem., Int. Ed.* **2003**, *42*, 4257. c) M. K. G. Mekhael, H. Heimgartner, *Helv. Chim. Acta* **2003**, *86*, 2805. d) D. Dhanak, S. Neidle, C. B. Reese, *Tertrahedron Lett.* **1985**, *26*, 2017. e) See ref. 4b. f) Y. Matsuda, M. Kitajima, H. Takayama, *Org. Lett.* **2008**, *10*, 125.

7 a) J. L. Namy, P. Girard, H. B. Kagan, *Nouv. J. Chim.* **1977**, *1*, 5. For reviews of SmI_2-mediated reactions, see: b) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307. c) K. Gopalaiah, H. B. Kagan, *New J. Chem.* **2008**, *32*, 607.

8 a) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, *104*, 3371. b) K. C. Nicolaou, S. P. Ellery, J. S. Chen, *Angew. Chem., Int. Ed.* **2009**, *48*, 7140.

9 a) J. L. Namy, J. Souppe, H. B. Kagan, *Tetrahedron Lett.* **1983**, *24*, 765. b) S.-i. Fukuzawa, A. Nakanishi, T. Fujinami, S. Sakai, *J. Chem. Soc., Chem. Commun.* **1986**, 624. c) T. Imamoto, S. Nishimura, *Chem. Lett.* **1990**, 1141. d) J. Inanaga, Y. Handa, T. Tabuchi, K. Otsubo, M. Yamaguchi, T. Hanamoto, *Tetrahedron Lett.* **1991**, *32*, 6557. e) N. Taniguchi, T. Hata, M. Uemura, *Angew. Chem., Int. Ed.* **1999**, *38*, 1232. f) Y. H. Kim, H. S. Park, D. W. Kwon, *Synth. Commun.* **1998**, *28*, 4517. g) J. M. Ready, S. E. Reisman, M. Hirata, M. M. Weiss, K. Tamaki, T. V. Ovaska, J. L. Wood, *Angew. Chem., Int. Ed.* **2004**, *43*, 1270.

10 Dimerization of carbodiimide by samarocene was reported, see: M. Deng, Y. Yao, Y. Zhang, Q. Shen, *Chem. Commun.* **2004**, 2742.

11 A. Williams, I. T. Ibrahim, *Chem. Rev.* **1981**, *81*, 589.

12 a) W. Ahrens, A. Berndt, *Tetrahedron Lett.* **1974**, *15*, 3741. b) G. Brunton, J. F. Taylor, K. U. Ingold, *J. Am. Chem. Soc.* **1976**, *98*, 4879.

13 T. Saito, K. Tsuda, Y. Saito, *Tetrahedron Lett.* **1996**, *37*, 209.

14 a) T. Saito, H. Ohmori, E. Furuno, S. Motoki, *J. Chem. Soc., Chem. Commun.* **1992**, 22. b) P. Molina, M. Alajarín, A. Vidal, P. Sánchez-Andrada, *J. Org. Chem.* **1992**, *57*, 929.

15 Compound **5a** was synthesized from 1-benzylpiperidine-2,4-dione by four steps: 1) Tf_2NPh, Et_3N, CH_2Cl_2, rt, 97%; 2) 2-aminophenylboronic acid pinacol ester, $[PdCl_2(PPh_3)_2]$, Na_2CO_3, H_2O, THF, reflux, 95%; 3) PhNCO, CH_2Cl_2, rt, 98%; 4) PPh_3, CBr_4, Et_3N, CH_2Cl_2, rt, 94%.

16 J. Inanaga, M. Ishikawa, M. Yamaguchi, *Chem. Lett.* **1987**, 1485.

17 a) R. S. Miller, J. M. Sealy, M. Shabangi, M. L. Kuhlman, J. R. Fuchs, R. A. Flowers, II, *J. Am. Chem. Soc.* **2000**, *122*, 7718. b) F. Machrouhi, B. Hamann, J.-L. Namy, H. B. Kagan, *Synlett* **1996**, 633.

18 Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-847381. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, U. K.; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

19 General procedures of reductive cyclizations; to solutions of samarium diiodide (0.1 M in THF, 2.4 mL) added a solution of 0.100 mmol carbodiimides and 21.0 µL *t*-BuOH in 2 mL THF in a dropwise manner (condition A) or to solutions of 0.100 mmol carbodiimide and 95.6 µL *t*-BuOH in 2 mL THF, were added solutions of samarium diiodide (0.1 M in THF, 2.1 mL) in a dropwise manner (condition B). After 15 min, saturated NH_4Cl(aq) were added and organic solvents were removed. The resultant aqueous solutions were extracted with AcOEt and the organic layers were washed with saturated NH_4Cl(aq), dried over Na_2SO_4, concentrated under reduced pressure. To solutions of 32.7 mg Boc_2O in 1 mL CH_2Cl_2, were added solutions of these crude materials in 2 mL CH_2Cl_2 at ambient temperature. 12.2 mg DMAP was added and the reaction mixtures were stirred for 5–20 h. The mixtures were evaporated and directly subjected to silica gel column chromatography to give iminoindolines.

