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Aryl Radical Cyclizations of 1-(2′-Bromobenzyl)isoquinolines with AIBN–Bu_3SnH: Formation of Aporphines and Indolo[2,1-*a*]isoquinolines

Kazuhiko Orito,* Shiho Uchiito, Yoshitaka Satoh, Takashi Tatsuzawa, Rika Harada, and Masao Tokuda

Laboratory of Organic Synthesis, Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

orito@org-mc.eng.hokudai.ac.jp

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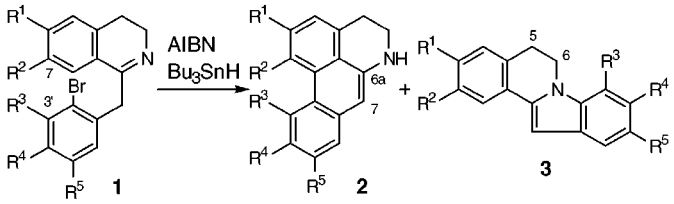
ABSTRACT



Radical cyclization of alkoxy-substituted 1-(2′-bromobenzyl)-3,4-dihydroisoquinolines 1 with AIBN–Bu_3SnH gave 6a,7-dehydroaporphines 2 preferentially. A steric repulsion between the respective alkoxy groups at the 7- and 3′-positions gave 5,6-dihydroindolo[2,1-*a*]isoquinolines 3 in a "disfavored" 5-*endo* cyclization mode. Radical cyclizations of the related substrates, such as 1-(2′-bromobenzoyl)isoquinolines or 1-(2′-bromo-α-hydroxybenzyl)isoquinolines, were also found to give the corresponding oxoaporphines or oxyaporphines.

A method for tin-mediated intramolecular aryl radical cyclization was reported by Beckwith in 1975.[1] Since then, focusing on the synthesis of benzocyclic compounds with biarylic and heterocyclic structures, various methods[2] based on intramolecular additions of aryl radicals onto aryl groups,[3] CC double bonds[4,5] (including enamines[6]), and CN or CO double bonds,[7] as well as the earlier discovery of photoinduced aryl−aryl couplings,[8] have been developed.

Radical cyclizations of 1-(2′-bromobenzyl)-1,2,3,4-tetrahydroisoquinolines have been reported to give aporphines.[3e,h,l] We have been interested in radical cyclization of 1-(2′-

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bromobenzyl)-3,4-dihydroisoquinolines, which will give us an answer as to whether the C═N group accepts a generated phenyl radical in a 5-*endo* cyclization mode. This paper deals with the competitive intramolecular additions of an aryl radical onto another aryl group vs onto a C═N group. The latter radical cyclization offers the first example of a "disfavored" 5-*endo* cyclization[9,10] of an aryl radical onto X═C bonds (Figure 1),[11] leading to the versatile benzocyclic systems shown below. New findings on the efficiency of

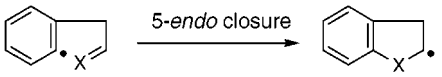
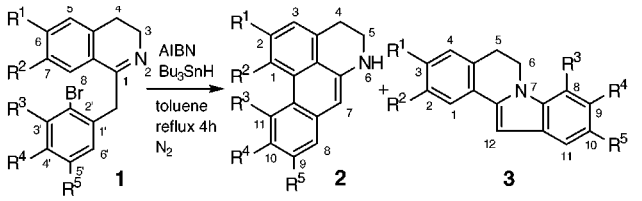


Figure 1.

aryl radical cyclizations in the related aporphine syntheses are also discussed.

First the substrates, alkoxy-substituted 1-(2′-bromo-benzyl)-3,4-dihydroisoquinolines **1a**−**i**, were prepared by Bischler−Napieralski cyclization of the corresponding acetamides,[12] and they were subjected to radical cyclization using a stoichiometric amount of AIBN (1 molar equiv) and Bu_3SnH (2 molar equiv) in boiling toluene (0.015 M) under nitrogen for 4 h (Scheme 1). Dihydroisoquinolines **1a**−**d**

Scheme 1



with a 2′-bromo-3′,4′-dialkoxybenzyl group at their C-1 position underwent an intramolecular aryl−aryl radical coupling at C-8 and/or a 5-*endo* cyclization on an N atom of the CN double bond to gave air-sensitive 6a,7-dehydroaporphines **2b**−**d**[13] and/or 5,6-dihydroindolo[2,1-*a*]-isoquinolines **3a**−**d**[12] almost quantitatively. The product ratios were determined by immediate ^{1}H NMR measurements of the crude products and are shown together with the isolated yields in Table 1. Compound **1a**, which has two vicinal dimethoxy groups at the 3′,4′- and 6,7-positions, did not give **2a** at all, but produced **3a** exclusively. Compounds **1b**−**d** gave **2b**−**d** and **3b**−**d** in ratios of 55:45, 30:70, and 60:40, respectively. These results are well accounted for by a large steric repulsion (a so-called buttressing effect[14]) between two vicinal dimethoxy groups at the 1,2- and 10,11-positions of the assumed aporphine **2a**.

In contrast, a similar treatment of **1e**−**h** which have no substituents at the 3′-position of the benzyl group preferentially gave the corresponding dehydroaporphines **2e**−**h**. Minor products, 5,6-dihydroindolo[2,1-*a*]isoquinolines **3e**−**h**, occurred in a 2,3,9,10-tetraalkoxy substitution pattern characteristic of the dibenzopyrrocoline alkaloids cryptaus-

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(12) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. *J. Org. Chem.* **1999**, *64*, 6583−6596.

(13) For reviews for the aporphine alkaloids, see: (a) Guinaudeau, H.; Leboeuf, M.; Cave, A. *Lloydia* **1975**, *38*, 275−338. (b) Guinaudeau, H.; Leboeuf, M.; Cave, A. *J. Nat. Prod.* **1979**, *42*, 325−360. (c) Kametani, T.; Honda, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1985; Vol. 24, pp 153−251.

(14) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1997**, *62*, 2604−2610 and references cited therein.

Table 1. Radical Cyclization of 1-(2′-Bromobenzyl)-3,4-dihydroisoquinolines **1**

substituent	product ratio[a] **2 : 3**	isolated yield[b] **2** and **3**
a: R^5=H, R^1=R^2=R^3=R^4=OMe	0 :100	0%, 68%
b: R^5=H, R^1=R^2=OMe, R^3+R^4=OCH_2O	55 : 45	42%,[c] 30%
c: R^5=H, R^1+R^2=OCH_2O, R^3=R^4=OMe	30 : 70	18%,[c] 52%
d: R^5=H, R^1+R^2= R^3+R^4=OCH_2O	60 : 40	29%,[c] 29%
e: R^3=H, R^1=R^2=R^4=R^5=OMe	90 : 10	62%, 3%
f: R^3=H, R^1=R^2=OMe, R^4+R^5=OCH_2O	90 : 10	79%, 7%
g: R^3=H, R^1+R^2=OCH_2O, R^4=R^5=OMe	90 : 10	55%, 7%
h: R^3=H, R^1+R^2= R^4+R^5=OCH_2O	85 : 15	45%, 7%
i: R^3=H, R^1=R^2=OMe, R^4=R^5=H	95 : 5	48%, 3%

[a] By ^{1}H NMR analysis of crude products. [b] Isolated by preparative TLC followed by recrystallizations (unoptimized). [c] Isolated by conversion to the corresponding oxoaporphine.

toline and cryptowoline.[15] Isoquinoline **1i** which has no alkoxy group on the benzyl group gave dehydroaporphine **2i** together with **3i** in a ratio of 11:1. This ratio is in good agreement with the results of the above-mentioned radical cyclizations of the R^3 = H series (**1e**−**h**).

In each case the corresponding debrominated reactant was not produced, although in the radical cyclizations of tetrahydroisoquinolines, regardless of the type of substituent on the N atom, such as an alkyl or acyl group, they have occurred as the regular byproducts in significant yields.[2,3] As depicted in Figure 2, this unique 5-*endo* ring closure into

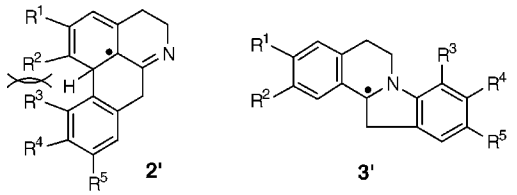
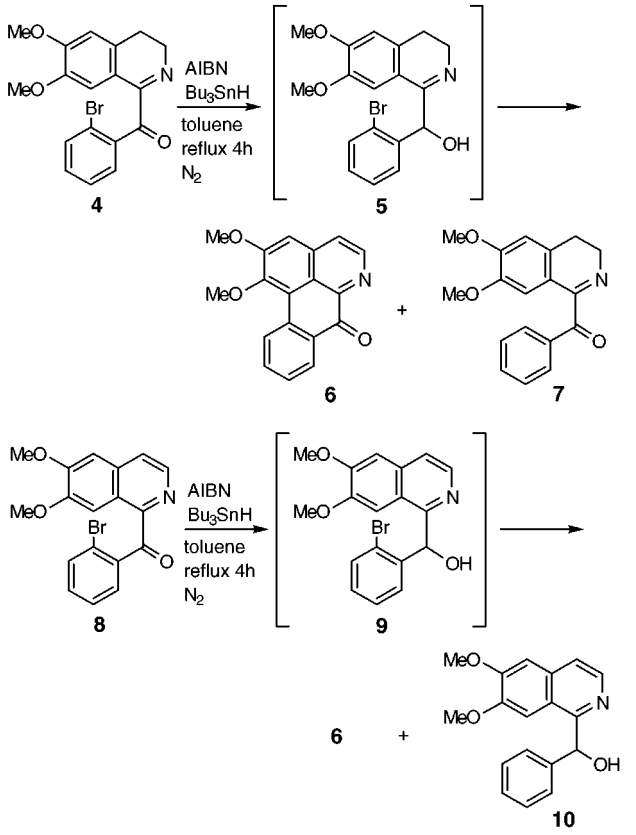


Figure 2.

indolo[2,1-*a*]isoquinolines is considered to be initiated mainly by the stabilization of radical **3′**, which is generated by addition of a phenyl radical onto a CN double bond, on a carbon bearing an N atom and an aryl group and to be completed by the formation of a double bond at the 12-position into **3**. Another radical species, **2′**, formed at a center of the conjugated system by aryl−aryl coupling in an 6-*exo* manner was transformed with the isomerization of the initial CN double bond into aporphine **2**.

Radical reactions of Δ^1-isoquinolines with a 1-benzoyl group, **4** and **8**, were next examined (Scheme 2 and Table

Scheme 2



2). Dihydroisoquinoline **4** gave oxoaporphine **6** together with the debrominated reactant (**7**) in a ratio of 46:31 in 77% conversion of **4** and in 40% and 18% isolated yields.

Table 2. Radical Cyclization of Compounds **4**, **8**, and **9**

substrate	product ratio[a] (isolated yield, %)[b] **4** : **6** : **7** : **9** : **10**
4	23 (12) : 46 (40) : 31 (18) : 0 : 0
8	0 : 58 (45) : 0 : 38 (28) : 4 (2)
9	0 : 62 (57) : 0 : 22 (15) : 16 (8)

[a] By ^{1}H NMR analysis of crude products. [b] Isolated by preparative TLC on silica gel followed by recrystallizations for **6**, **7**, **9** and **10**.

Isoquinoline **8** also gave **6** together with alcohol **9** and the debrominated alcohol **9** (**10**) in a ratio of 58:38:4 (45, 28 and 2% yields). A similar treatment of ketone **8** without AIBN gave alcohol **9**. Radical reaction of the isolated **9**[16]

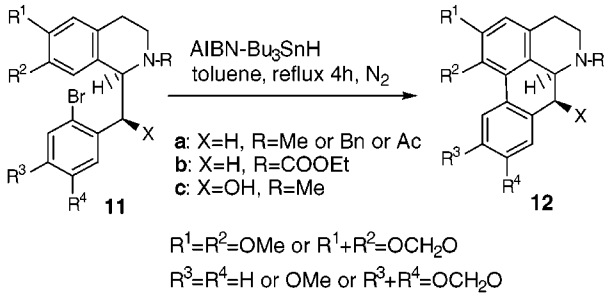
(15) For a review of the dibenzopyrrocoline alkaloids, see: Eliott, I. W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1987; Vol. 31, pp 101−116.

(16) Compound **9**: colorless crystals; mp 143−145 °C (benzene−hexane); IR (Nujol) 3477−3370, 1510 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.88 (s, 3H), 3.99 (s, 3H), 6.71 (s, 1H), 6.88−6.69 (m, 1H), 7.05−7.13 (m, 4H), 7.54 (d, J = 5.6 Hz, 1H), 7.61−7.64 (m, 1H), 8.41 (d, J = 5.6 Hz, 1H); EI-MS *m*/*z* (rel intensity) 373 (M^+, 14), 294 [$(M - Br)^+$, 100], 278 (12), 262 (5).

also gave oxoaporphine **6** (57%), and in this case the amount of unchanged **9** was smaller (62:22:16) compared with that obtained by an identical treatment of **8**, proving that a significant amount of Bu_3SnH was consumed for reduction of **8** to **9** prior to the radical cyclization. A similar Bu_3SnH treatment converted **4** more easily, even at room temperature, to labile alcohol **5**,[17] which on exposure to air was oxidized back to **4** quantitatively. Thus, in this radical cyclization of 1-(2′-bromobenzoyl)-Δ^1-isoquinoline **4** or **8**, a coupling between an imine nitrogen and a 2′ carbon did not occur, but oxoaporphines were formed in good yields probably along the main pathway via the alcohol **5** or **9**.[18]

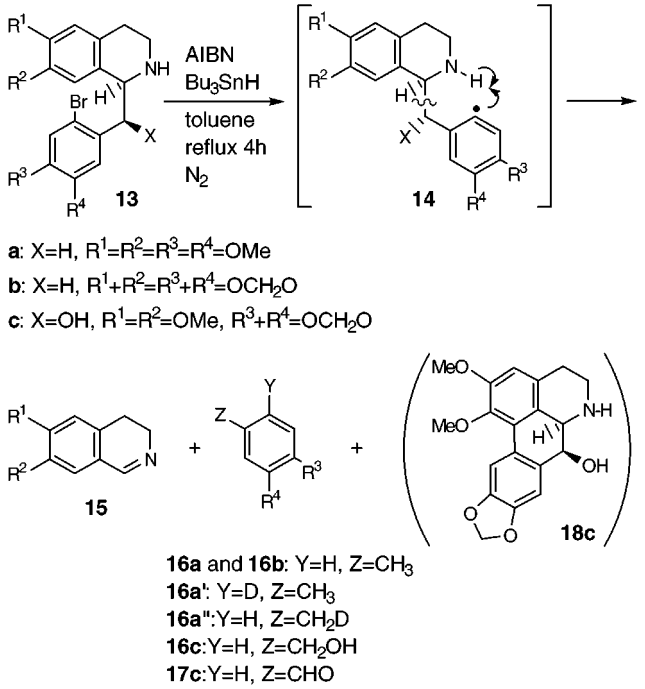
Radical cyclizations of 1-benzyltetrahydroisoquinolines have been reported by Castedo's and Comins' groups.[3e,h,l] Reexamination under our conditions as described above gave rather similar results. All the substrates of type **11a** (X = H) gave aporphines **12a** in 22−35% yields, together with the respective debrominated reactants. Substrates **11b** (X = H) which have a more bulky N-substituent, such as a COOEt group, gave the corresponding aporphine **12b** in 50% yield. Substrates **11c** which have an *N*-methyl and an α-hydroxy group (X = OH) gave oxyaporphines **12c** in 57−68% yields. The intramolecular hydrogen bonding between the α-OH and an N atom[8j] as well as the steric block with a substituent on the N atom is considered to work for the aryl radical coming close to a benzene ring of the isoquinoline part, reflecting the enhanced yields for **12b** and **12c**. This fixed conformation is in agreement with the above-mentioned reaction mechanism for the radical cyclization of **4** and **8** via benzyl alcohols **5** and **9**.

Scheme 3



In contrast, radical cyclizations of tetrahydroisoquinolines (**13a**,**b**, X = H) with no substituent on the N atom were unsuccessful,[3f] and they gave 3,4-dihydroisquinoline **15** (60%) and toluene **16a** or **16b** (60%). The reaction mechanism based on a hydrogen abstraction from the isoquinoline

Scheme 4



N-H group by an aryl radical was easily proved by a deuterium incorporation experiment. As shown in Scheme 4, when the radical reaction of **13a** was carried out using Bu_3SnD, toluene-*2-d* **16a′** was obtained, and the radical reaction using Bu_3SnH of the N-D derivative of **13a** gave toluene-α-*d* **16a″**. From **13c** (X = OH), **15** (77%), benzyl alcohol **16c** (45%), and benzaldehyde **17c** (10%) were obtained as the main products, and as expected, the corresponding oxyaporphine **18c** was also produced in 14% yield,[8i,l] suggesting again the occurrence of the above-mentioned hydrogen bonding.

In summary, radical cyclization of alkoxy-substituted 1-(2′-bromobenzyl)-3,4-dihydroisoquinolines with AIBN−Bu_3SnH gave 6a,7-dehydroaporphines preferentially owing to an aryl−aryl coupling. A steric repulsion between the respective alkoxy groups at the 7- and 3′-positions induced an aryl−imino coupling in a "disfavored" 5-*endo* cyclization mode to give 5,6-dihydroindolo[2,1-*a*]-isoquinolines. Radical cyclizations of the related substrates, such as 1-(2′-bromobenzoyl)isoquinolines and their 3,4-dihydro and 1-(2′-bromobenzyl)-1,2,3,4-tetrahydo derivatives, were found to give the corresponding oxoaporphines or oxyaporphines being directed by the steric bulk of the N-substituents and hydrogen bonding between an OH group at the α-position and the N atom.

Supporting Information Available: Characterization data for products **2**, **3**, **4**, **6**, **9** **12**, and **18c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Compound **5**: a colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.27−2.77 (m, 2H), 3.65−3.72 (m, 1H), 3.76 (s, 3H), 3.87 (s, 3H), 4.03−4.13 (m, 1H), 6.21 (d, J = 2.3 Hz, 1H), 6.67 (s, 1H), 6.79 (s, 1H), 7.07−7.20 (m, 3H), 7.56−7.60 (m, 1H).

(18) This is also proved by the fact that the photoinduced cyclization, which has no hydride reagent, of a bromide similar to **4** was unsuccessful. See ref 8i.