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Aryl Radical Cyclizations: One-Pot Syntheses of Protoberberine and Pavine Alkaloids

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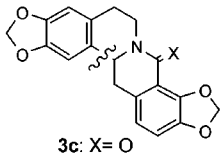
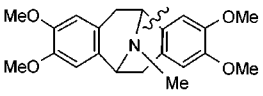
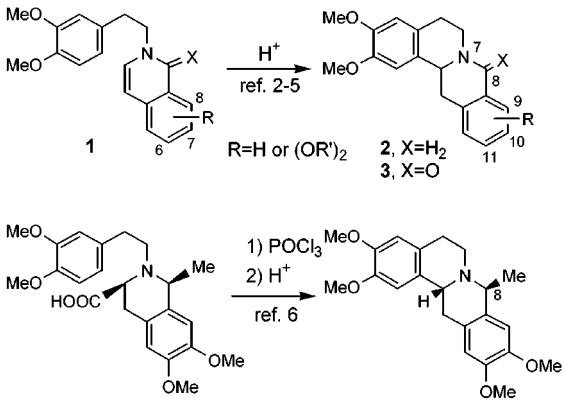
ABSTRACT





Treatment of 2-(2′-bromo-β-phenethyl)isocarbostyrils 7 with AIBN–Bu_3SnH in boiling benzene gave 8-oxoberbines 3 in good yields. A similar treatment of 2-(2′-bromo-β-phenethyl)isoquinolinium bromides 6 and their nor- and homoanalogues (10, 11) induced 6-, 5-, and 7-*exo* radical closures in a one-pot manner to give protoberberines 2, dibenzo[*b,g*]indolizidine 14a and, dibenzo[*a,h*]-1-azabicyclo[5.4.0]undecane 15a, respectively. A one-pot radical cyclization of 1-(2′-bromobenzyl)isoquinoline methiodide 18a gave a pavine alkaloid, (±)-algemonine (19a).

Berbines and 8-oxoberbines possess a variety of physiological activities, including antitumor and anticancer activities.[1] Acid-catalyzed cyclizations of 1,2-dihydroisoquinolines **1** (X = H_2) to berbines **2** and isocarbostyrils **1** (X = O) to 8-oxoberbines **3** were studied by Huffman,[2] Battersby,[3] and Dyke[4] in the period 1960−1966. In 1970, Govindachari[5] reported the application of those methods to the synthesis of protoberberine alkaloids. In 1978, Rapoport[6] reported an improved method, which starts with phenylalanine derivatives, and its application to the synthesis of 8- or 13-methylberbine. However, the methods for preparation of 8-oxoberbines having alkoxy-substituents on the D-ring seem to be somewhat inefficient because of the decreased electrophilicity of an alkoxy-substituted isoquinoline ring of the corresponding reactants.[4,5]



On the basis of the results of our study on intramolecular aryl radical cyclizations[7] involving an aryl−aryl or aryl−

(1) See refs 3 and 12 cited in Matulenko, M. A.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 573−580.
(2) Huffman, J. W.; Miller, E. G. *J. Org. Chem.* **1960**, *25*, 90−92.
(3) Battersby, A. R.; LeCount, D. J.; Garrant, S.; Thrift, R. I. *Tetrahedron* **1961**, *14*, 46−53.
(4) Brown, D. B.; Dyke, S. F. *Tetrahedron* **1966**, *22*, 2429−2435.
(5) Govindachari, T. R.; Nagarajan, K.; Charubala, R.; Pai, R. *Ind. J. Chem.* **1970**, 763−765.
(6) Dean, T. R.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 2115−2122, 4183−4189.
(7) For a review, see: Banik, B. K. *Curr. Org. Chem.* **1999**, *3*, 469−486.

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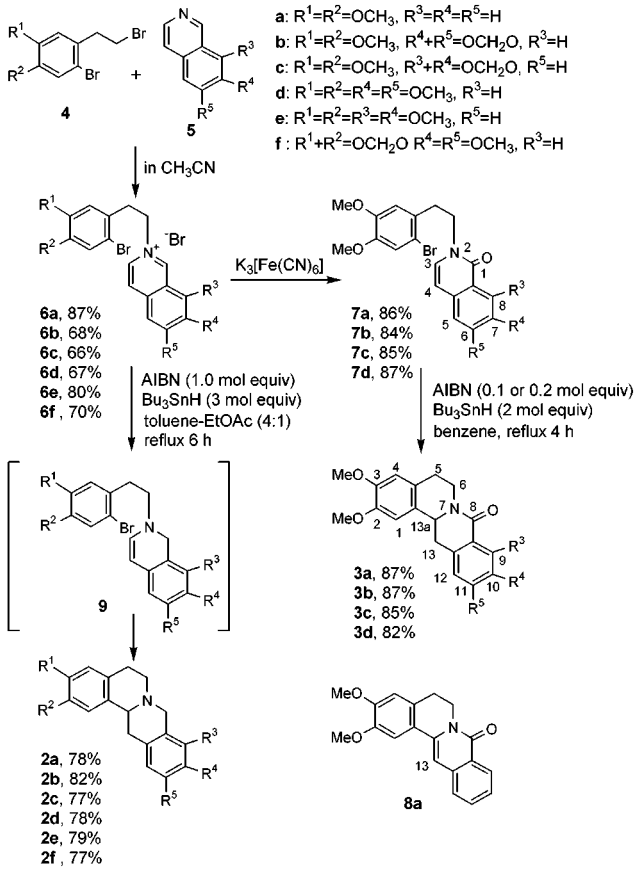
imino coupling,[8] we expected that an intramolecular aryl radical−enamine double-bond coupling would be a useful method for resolving the abovementioned disadvantages. Thus, the efficiency of this method for the preparation of isoquinoline, indoline, and 2-benzazepine ring systems and the applicability to a one-pot synthesis of protoberberine and pavine alkaloids were investigated.

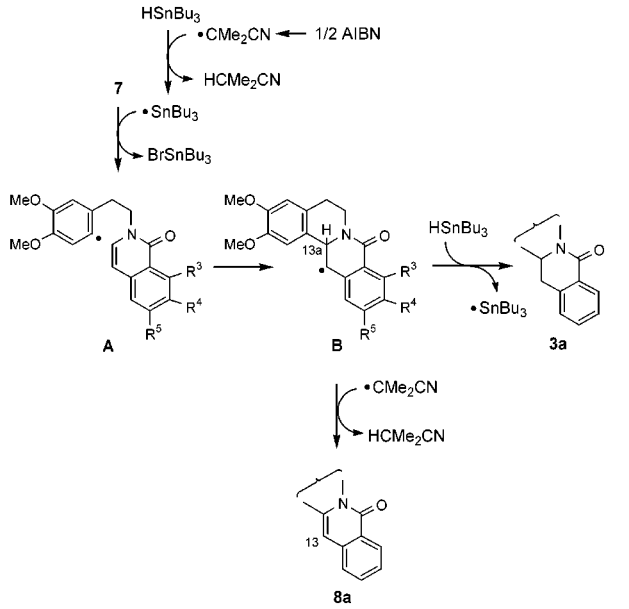
First, we examined a radical cyclization of non-alkoxy-substituted isocarbostyril **7a**, which was prepared according to the method reported by Dyke for isocarbostyril **1** (X = O, R = H).[4] Treatment of **7a** with AIBN (0.1 mol equiv) and Bu_3SnH (2 mol equiv) in boiling benzene for 3 h gave 8-oxoberbine **3a** exclusively (87% isolated yield) (Scheme 1). An alternative treatment using excess AIBN (1.0 mol equiv) gave 13,13a-dehydro derivative of **3a** (**8a**)[2] as the byproduct in a 85:15 ratio for **3a** and **8a**, respectively. This dehydro compound was probably formed in the presence of excess AIBN via a hydrogen abstraction at the C-13 position with an isobutyronitrile radical from radical **B**, which was formed by an intramolecular addition of radical **A**. 8-Oxoberbine **3a** was formed by another hydrogen abstraction from Bu_3SnH, as shown in Scheme 2. Alkoxy-substituted bromoisocarbostyrils **7b**, **7c,** and **7d** (6′-bromo derivative of **1**, X = O), which were easily prepared by heating the corresponding isoquinolines and β-phenethylbromide, followed by treatment of the resultant isoquinolinium salts **6** with an aqueous solution of $K_3[Fe(CN)_6]$ and KOH, were subjected to radical cyclization [AIBN (0.2 mol equiv) and Bu_3SnH (2 mol equiv) in boiling benzene for 3 h] to give 8-oxoberbines **3b** (87%), **3c** (85%), and also **3d** (82%) in good yields (Scheme 1).[9] No debrominated reactants were obtained in each case. Hydride reduction of 8-oxoberbines **3** has been known to give the corresponding protoberberines.[10]

The above method was applied to the direct synthesis of protoberberine bases and their regioisomers from the salts **6**. Bu_3SnH has been known to work not only as a radical initiator but also as a mild reducing agent.[11−13] When isoquinolinium salt **6a** was refluxed with Bu_3SnH (1 mol equiv) in toluene and EtOAc (4:1) for 4 h, 1,2-dihydroisoquinoline **9** was quantitatively obtained (Scheme 1). A one-pot radical cyclization of isoquinolinium salt **6a** was thus carried out using AIBN (1.0 mol equiv) and Bu_3SnH (3 mol equiv) in the same solvent system to give **2a** in 78% yield. Protoberberine alkaloids (±)-sinactine (**2c**), (±)-xylopinine (**2d**), (±)-tetrahydropalmatine (**2e**), and their regioisomers, **2b** and **2f**, were also produced in similar manners using a solvent system of toluene and CH_3CN (1:1) [toluene and EtOAc (4:1) for **2d**] in 77−82% yields. 13,13a-Dehydroberbines corresponding to **8a** were not detected, but the

Scheme 1



Scheme 2



(8) Orito, K.; Uchiito, S.; Satoh, Y.; Tatsuzawa, T.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 307−310.

(9) It has been reported that the acid-catalyzed cyclization of 6,7-dimethoxy isocarbostylril **1** (X = O) failed to give **3d** (ref 4), and (±)-8-oxosinactine (**3c**) was obtained in a low yield (ref 5).

(10) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. *J. Org. Chem.* **1999**, *64*, 6583−6596, and references cited therein.

(11) Kuivila, H. G. *Synthesis* **1970**, 499−4509.

(12) Yamaguchi, R.; Hanasaki, T.; Uchimoto, K. *Chem. Lett.* **1988**, 913−916.

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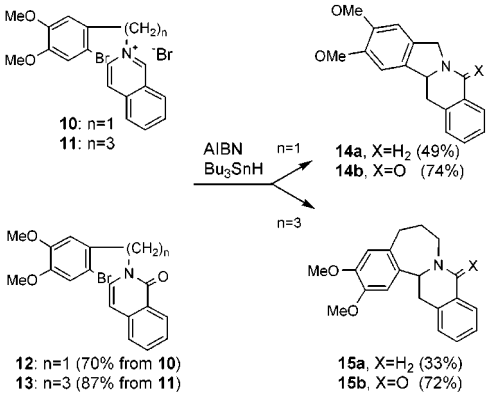
debromo derivatives of **9** (**1**, X = H_2) were formed as the byproducts in small amount.

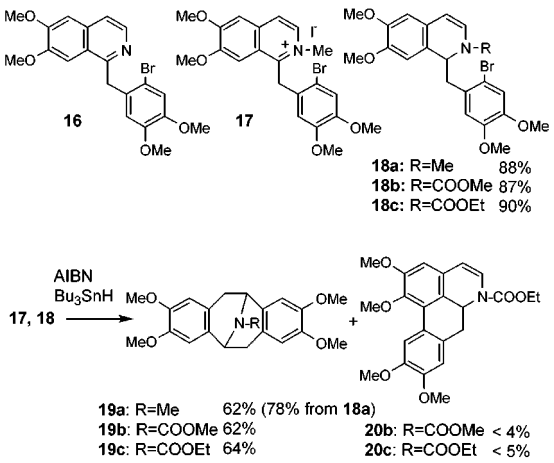
Nor- and homosalts, **10** and **11**, were also subjected to the one-pot radical cyclization [AIBN (1 mol equiv) and Bu_3SnH (3mol equiv), toluene−CH_3CN (4:1), 4 h] to give dibenzo[*b,g*]indolizidine **14a** (49%) and dibenzo[*a,h*]-1-azabicyclo[5.4.0]undecane **15a** (33%) (Scheme 3), accompanied by the 1,2-dihydro derivatives of the debrominated reactants. Their 8-oxo derivatives, **14b** and **15b**, were obtained in better yields (74% and 72%, respectively) by the radical cyclization [AIBN (0.1 mol equiv) and Bu_3SnH (2 mol equiv), benzene, 4 h] of isocarbostyrils **12** and **13**, which were prepared in 70% and 87% yields from the salts **10** and **11**, respectively.

Scheme 3



Next, we describe the synthesis of pavine alkaloid (Scheme 4), which has a unique dibenzo-9-azabicyclo-[3.3.1]nonane structure.[14] It is of interest whether an aryl radical generated from 1-(2′-bromobenzyl)-1,2-dihydroiso-quinolines **18** adds to the double bond at the 3 position or prefers an aryl−aryl coupling similar to the radical cyclizations of analogous systems, such as 1,2,3,4-tetrahydro- and 3,4-dihydroisoquinolines, which give aporphines and dehydroaporphines. A sparingly soluble 2′-bromopapaverine[15] methiodide **17** was converted to its 1,2-dihydro derivative **18a** by treatment with $LiAlH_4$ in DME at 0 °C for 2 h (88%) or almost quantitatively with Bu_3SnH (3 mol equiv) in a boiling toluene containing DMF (1:1) for 4 h. When this bromide **18a** was heated with AIBN (1 mol equiv) and Bu_3SnH (2 mol equiv) in toluene−DMF (3:1) for 4 h, the desired pavine alkaloid, (±)-*N*-methylpavine **19a** [(±)-argemonine],[16] was obtained as the only cyclization product in 78% isolated yield, and no aporphine was detected. Although attempts to execute a one-pot transformation of the salt **17** to **19a** by adding all of the reagents at once failed, the step-by-step treatment of a boiling suspension of **17** in DMF−toluene (1:3) with Bu_3SnH (1 mol equiv) for 1 h and successively with AIBN (1 mol equiv) and Bu_3SnH (2 mol equiv) for 4 h gave **19a** in 62% isolated yield. Treatment of **16** with Bu_3SnH (1 equiv) in CH_3CN at 0 °C for 5 min and then ClCOOMe or ClCOOEt (1.2 equiv) at 0−20 °C for 3 h gave carbamate **18b** or **18c** (87% or 90%, respectively), which was then subjected to radical cyclization using AIBN (0.1 mol equiv) andBu_3SnH (2 mol equiv) to give methoxy- and ethoxycarbonylpavines **19b** or **19c**[17] in isolated yields of 62% and 64%, respectively. In these reactions, aporphines, **20b** and **20c**, were formed as byproducts in less than 1/10 product ratios, owing to an aryl−aryl coupling probably induced by the steric effect of a more bulky N-substituent.[8] These product ratios (94:6 for **19b** and **20b** and 90:10 for **19c** and **20c**) both changed to 80:20, when 1 mol equiv of AIBN was used.

Scheme 4



In summary, we have demonstrated a new and convenient method for synthesis of protoberberine[18] and pavine alkaloids based on an intramolecular aryl radical addition.

Supporting Information Available: Characterization data for compounds **4**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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