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A Facile Route to Indolo[2,1-*a*]isoquinolines and Dibenzopyrrocoline Alkaloids

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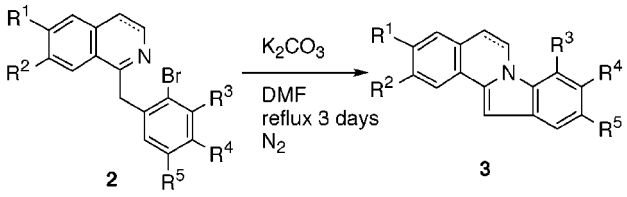
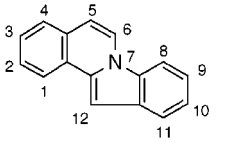
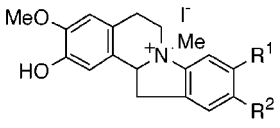
ABSTRACT



Treatment of 1-(2′-bromobenzyl)-3,4-dihydroisoquinolines 2 in the presence of K_2CO_3 in boiling DMF efficiently provided a variety of alkoxy-substituted indolo[2,1-*a*]isoquinolines 3. Application of this cyclization to 7-benzyloxyisoquinoline derivatives, followed by further elaboration of the resultant 2-benzyloxy-5,6-dihydroindolo[2,1-*a*]isoquinolines 16a,b, led to the formal synthesis of dibenzopyrrocoline alkaloids, (±)-cryptaustoline (1a) and (±)-cryptowoline (1b).

Indolo[2,1-*a*]isoquinoline has a unique nitrogen-containing tetracyclic structure, characteristic of dibenzopyrrocoline alkaloids, cryptaustoline **1a** and cryptowoline **1b**, isolated





1a: cryptaustoline R^1=R^2=OMe
1b: cryptowoline R^1+R^2=OCH_2O

from the bark of *Cryptocarya bowiei*.[1,2] Several methods for construction of this structure,[3−8] including the well-known benzyne reaction[3] or oxidative coupling[4] of 1-benzylisoquinolines, have been reported. Antileukemic and antitumor activities of such bases have been reported, and their ammonium salts have been expected to enhance the activities.[3I,9]

As shown in Scheme 1, we initially encountered this structure in the intramolecular cyclization products of *erythro*-1-[(2′-bromopheny)hydroxymethyl]-1,2,3,4-tetrahydroisoquinolines **5**, which were prepared in three more

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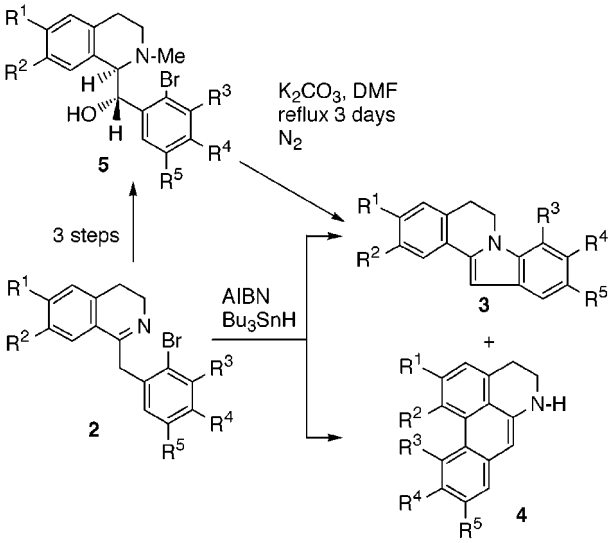
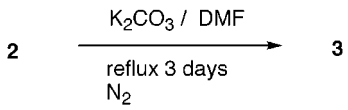
Scheme 1. Preceding Studies[10−12]



steps of reactions from 2′-bromobenzyl-3,4-dihydroisoquinolines **2**, in the presence of K_2CO_3.[10,11] Recently, we reported Bu_3SnH-induced aryl radical cyclization, which competitively gave 5,6-dihydroindolo[2,1-*a*]isoquinolines **3** and aporphines **4** from **2**.[12] In the present study, we developed a convenient method for selective preparation of a variety of alkoxy-substituted indolo[2,1-*a*]isoquinolines **3** from the same substrates **2**, involving **3a**−**d**, which cannot be obtained by the benzyne method noted above.[3]

Scheme 2. Synthesis of 5,6-Dihydroindolo[2,1-*a*]isoquinolines **3**



entry	isolated yields and mps of **3**	
R^5=H		
2a: R^1=R^2=R^3=R^4=OMe	95 %	mp 193-195 °C (A)
2b: R^1=R^2=OMe, R^3+R^4=OCH_2O	92 %	mp 198-200 °C (B)
2c: R^1+R^2=OCH_2O, R^3=R^4=OMe	78 %	mp 177-180 °C (B)
2d: R^1+R^2= R^3+R^4=OCH_2O	95 %	mp 205-206 °C (A)
R^3=H		
2e: R^1=R^2=R^3=R^4=OMe	95 %	mp 207-208 °C (C)[a]
2f : R^1=R^2=OMe, R^3+R^4=OCH_2O	95 %	mp 241-242.5 °C (C)
2g: R^1+R^2=OCH_2O, R^3=R^4=OMe	89 %	mp 212-216 °C (C)
2h: R^1+R^2= R^3+R^4=OCH_2O	79 %	mp 214-217.5 °C (C)
2 i: R^1=R^2=OMe, R^4=R^5=H	83 %	mp 177.5-179.5 °C (B)
2 j: R^1+R^2=OCH_2O, R^4=R^5=H	76 %	mp 189-193.5 °C (B)

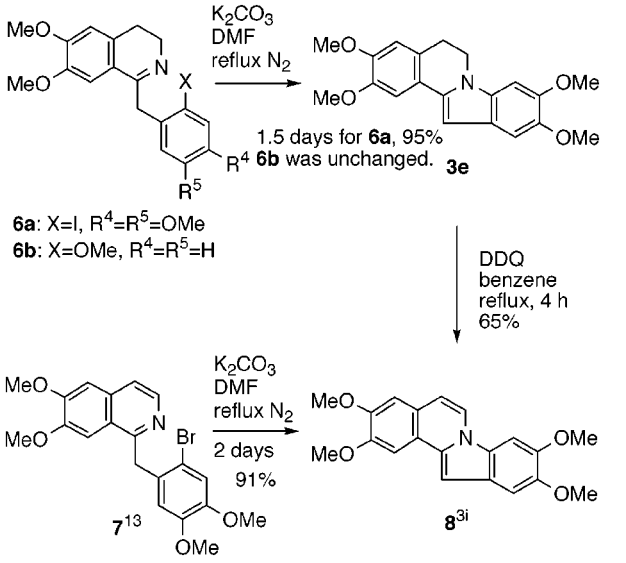
Solvents for crystallization: A, EtOH; B, MeOH-CH_2Cl_2; C, MeOH-Et_2O

a: lit.[1] mp 199 °C; [4a] 201-203 °C; [3d] 202-203 °C; [3a] 202-204 °C; [8,10] 204-205 °C; [3g,i] 209-210 °C

When substrates **2a**−**d** with an alkoxy group at their 3′ position or substrates **2e**−**j** without the alkoxy group, including the compounds **2i** and **2j** having no substituent on the phenyl group except for a Br atom, were heated in the presence of 2 mol equiv of K_2CO_3 in boiling DMF for 3 days (Scheme 2), the corresponding 5,6-dihydroindolo[2,1-*a*]isoquinolines **3** were obtained in 76−95% isolated yields by crystallization. Dimeric products at their C-12 position were not detected at all.[3g,4c,7b] The cyclization did not proceed without alkali. K_3PO_4 worked well, similarly to K_2CO_3, but stronger bases such as BuLi and KO^{t}Bu, did not. Replacement of DMF with DMSO resulted in the formation of a black tar.

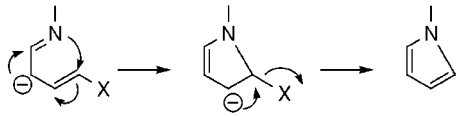
Under the same conditions, the 2′-iodo derivative **6a** was consumed much faster than the bromide **2a**, and the cyclization finished within 1.5 days. However, its 2′-methoxy derivative **6b** was recovered unchanged. The cyclization of a readily accessible 3′-bromopapaverine **7**[13] also proceeded smoothly to give a fully aromatized indolo[2,1-*a*]isoquinoline **8**, mp 225.5−228.0 °C (MeOH, lit.[3i] mp 210 °C), within 2 days quantitatively (Scheme 3), although DDQ oxidation of **3e** gave **8** (65%).

Scheme 3. Synthesis of Indolo[2,1-*a*]isoquinoline **8**



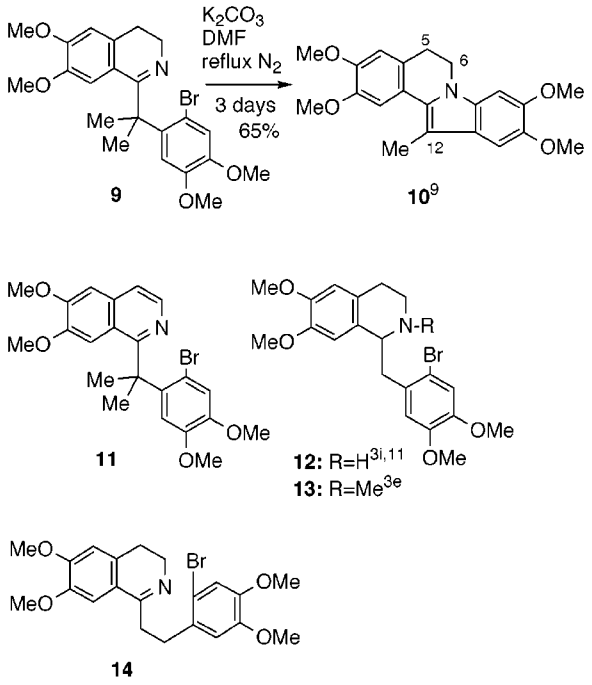
It had been reported that the thermal electrocyclization of a pentadienyl anion gave a cyclopentenyl anion.[14] We had assumed that such an effect might have contributed to these cyclizations (Scheme 4), until the following fact was disclosed. 1-Benzyldihydroisoquinoline **9**, having two methyl

Scheme 4. An Assumed Thermal Electrocyclization Process[12]



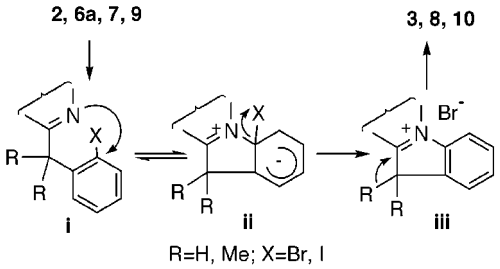
groups at the benzyl position, also underwent a similar cyclization with loss of one methyl group to give 12-methylindolo[2,1-*a*]isoquinoline **10**, mp 224−226 °C (MeOH−CH_2Cl_2, lit.[9] 216−217 °C) (Scheme 5). The dehydro derivative (**11**) did not cyclize and was recovered unchanged. The dihydro derivatives of **2e**, 1,2,3,4-tetrahydroisoquinolines (**12**, **13**),[11] were also recovered unchanged. An attempt to produce a quinoline ring using the homologue **14** failed, and it was recovered unchanged. On the basis of these results, a reaction pathway via **i**, **ii**, and **iii** (Scheme 6) which starts with a nucleophilic addition of the isoquinoline nitrogen and ends up in the formation of a stable conjugated system, "indole ring", was proposed for this versatile cyclization.

Scheme 5. Formation of Indolo[2,1-*a*]isoquinoline **10**

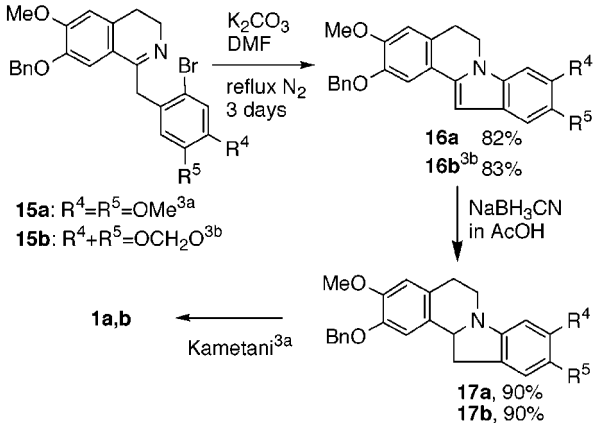


Application of this cyclization on 7-benzyloxy-3,4-dihydroisoquinoline **15a**[3a] and **15b**[3b] gave 5,6-dihydroindolo[2,1-*a*]isoquinolines **16a**, mp 146−148 °C (MeOH), and **16b**, mp 159−161 °C (MeOH, lit.[3b] mp 157−158 °C), almost quantitatively (82% and 83% isolated yields by crystallization). Dihydroisoquinolines **16a** and **16b** were further converted by treatment with excess $NaBH_3CN$ in AcOH almost quantitatively to air-sensitive tetrahydroindolo[2,1-*a*]isoquinolines **17a** and **17b**, respectively (Scheme 7). In view of the previous conversion of these compounds into (±)-cryptaustoline (**1a**) and (±)-cryptowoline (**1b**),[3a,b,i,7b] this constitutes a formal synthesis of the alkaloids.

Scheme 6. A Probable Pathway to Indolo[2,1-*a*]isoquinolines **3**, **8**, and **10**



Scheme 7. Synthesis of Dibenzopyrrocoline Alkaloids Cryptaustoline **1a** and Cryptowoline **1b**



Supporting Information Available: Characterization data for products **3**, **8**, **10**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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