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A New Route to Benzo[a]quinolizine Derivative by the Intramolecular Radical Cyclization

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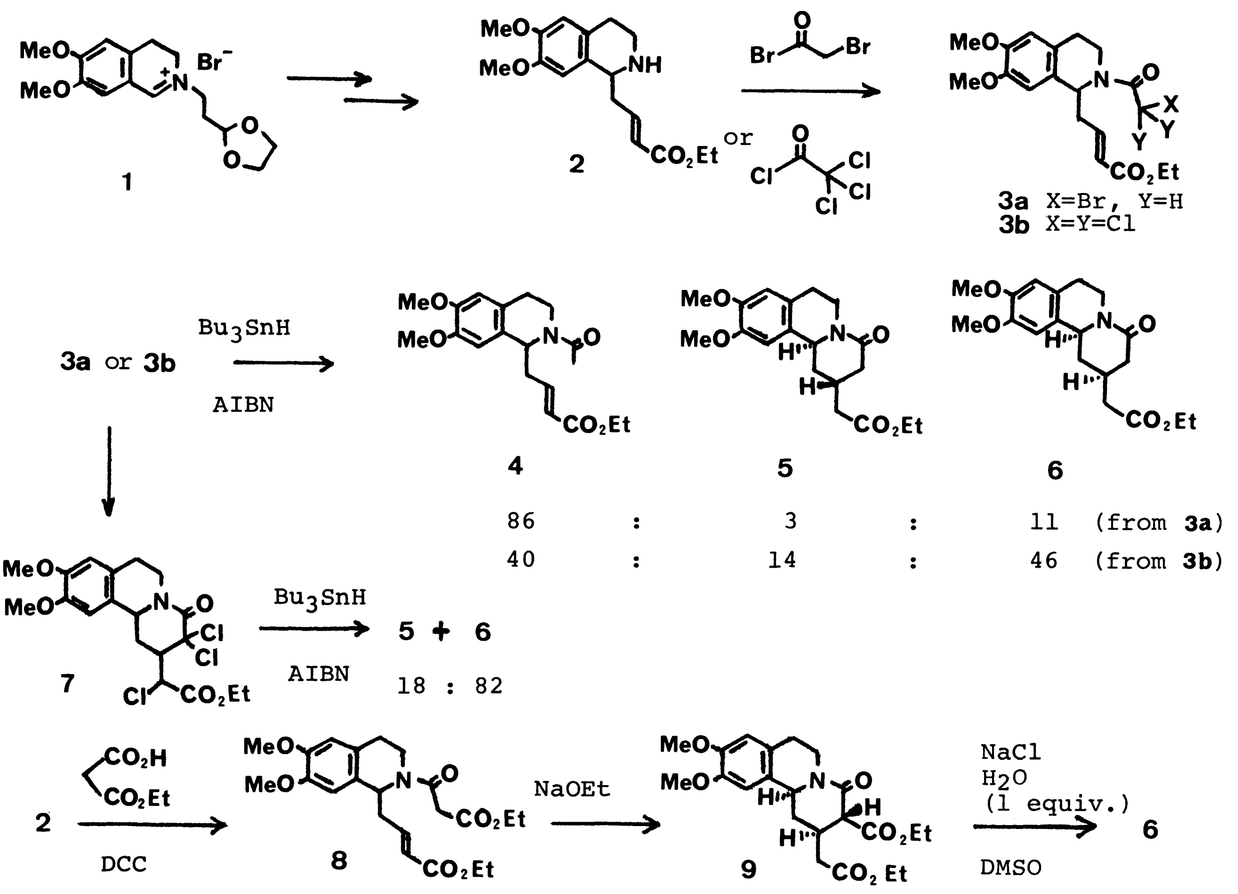
A synthesis of benzo[a]quinolizine derivatives by the radical cyclization of N-α-haloacetylisoquinoline compound is described.

In approaches to the synthesis of emetine, which possesses biological activity, a variety of the synthetic methods of benzo[a]quinolizines have been developed.[1] Recently, potential utility of an intramolecular radical cyclization for a regio- and stereoselective carbon-carbon bond formation was explored.[2] We have examined the radical cyclization of N-α-haloacetylisoquinoline compound (**3**) in connection with our interests in a stereoselective synthesis of emetine and the related alkaloids. The results of our studies are described in this paper.

Condensation of **2**, which was prepared from the iminium salt (**1**) in 2 steps as mentioned previously,[3,4] with bromoacetyl bromide gave **3a** in 54% yield. Similarly, **3b** was obtained by the condensation of **2** with trichloroacetyl chloride in 66% yield. Both **3a** and **3b** were subjected to radical cyclization. A mixture of **3a** and tributyltin hydride (Bu_3SnH) in dry benzene in the presence of α,α'-azobis-isobutyronitrile (AIBN) was heated under reflux to give **4**, **5**, and **6** in a ratio of ca. 86:3:11 (96% yield).[5] Radical cyclization of **3b** under the same conditions gave **4**, **5**, and **6** in a ratio of ca. 40:14:46 (97% yield). The stereochemistry of **6** was determined by an alternative synthesis as follows. The compound **8**, which was readily prepared by the condensation of **2** with monoethyl malonate, was cyclized by treating with sodium ethoxide in dry ethanol to give the tricyclic compound (**9**) in 63% yield.[3] Deethoxycarbonylation of **9** was effected by heating in dimethyl sulfoxide in the presence of NaCl and 1 equiv. H_2O to furnish **6**, in 47% yield, whose spectral data were identical with those of the sample prepared above.

On the other hand, an acetonitrile solution of **3b** containing CuCl(0.3 mol%)[6] was heated at 140 °C in a sealed tube to give the cyclic compound **7** in 98% yield. Dehalogenation of **7** using Bu_3SnH in dry benzene in the presence of AIBN afforded **5** and **6** in 95% yield in a ratio ca. 18:82.

Conversion of **6** to emetine via the thio-Claisen rearrangement[7] and further application of this method to the synthesis of the indole compounds are now in progress.



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5) All new compounds gave satisfactory 200 MHz NMR, IR, and high resolution mass and/or elemental data. **6**: IR (film) 1730, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, J=6Hz, $OCH_2\underline{Me}$), 2.0-3.0(9H, m), 3.87(6H, s, MeO x 2), 4.19(2H, q, J=6Hz, $OC\underline{H}_2Me$), 4.64-4.96(2H, m, C_6-H_{eq} and C_{11b}-H), 6.62(1H, s, ArH), 6.66(1H, s, ArH) High resolution mass. Calcd for $C_{19}H_{25}NO_5$: 346.1653. Found: 346.1632.

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